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<p>(21) International Application Number: PCT/US96/14674</p> <p>(22) International Filing Date: 30 August 1996 (30.08.96)</p> <p>(30) Priority Data:</p> <table> <tr> <td>08/523,436</td> <td>1 September 1995 (01.09.95)</td> <td>US</td> </tr> <tr> <td>08/533,634</td> <td>22 September 1995 (22.09.95)</td> <td>US</td> </tr> <tr> <td>08/620,874</td> <td>22 March 1996 (22.03.96)</td> <td>US</td> </tr> <tr> <td>08/659,683</td> <td>5 June 1996 (05.06.96)</td> <td>US</td> </tr> <tr> <td>08/680,574</td> <td>12 July 1996 (12.07.96)</td> <td>US</td> </tr> </table> <p>(71) Applicant: CORIXA CORPORATION [US/US]; Suite 464, 1124 Columbia Street, Seattle, WA 98104 (US).</p> <p>(72) Inventors: REED, Steven, G.; 2843 - 122nd Pine Place N.E., Bellevue, WA 98005 (US). SKEIKY, Yasir, A., W.; 8327 - 25th Avenue N.W., Seattle, WA 98117 (US). DILLON, Davin, C.; 21607 N.E. 24th Street, Redmond, WA 98053 (US). CAMPOS-NETO, Antonio; 9308 N.E. Midship Court, Bainbridge Island, WA 98110 (US). HOUGHTON, Raymond; 2636 - 242nd Place S.E., Bothell, WA 98021 (US). VEDVICK, Thomas, H.; 1301 Spring Street, Seattle, WA 98104 (US). TWARDZIK, Daniel, R.; 10195 South Beach Drive, Bainbridge Island, WA 98110 (US).</p>		08/523,436	1 September 1995 (01.09.95)	US	08/533,634	22 September 1995 (22.09.95)	US	08/620,874	22 March 1996 (22.03.96)	US	08/659,683	5 June 1996 (05.06.96)	US	08/680,574	12 July 1996 (12.07.96)	US	<p>(74) Agents: MAKI, David, J. et al.; Seed and Berry L.L.P., 6300 Columbia Center, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i> </p>																										
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<p>(54) Title: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND DIAGNOSIS OF TUBERCULOSIS</p> <p>(57) Abstract</p> <p>Compounds and methods for inducing protective immunity against tuberculosis are disclosed. The compounds provided include polypeptides that contain at least one immunogenic portion of one or more <i>M. tuberculosis</i> proteins and DNA molecules encoding such polypeptides. Such compounds may be formulated into vaccines and/or pharmaceutical compositions for immunization against <i>M. tuberculosis</i> infection, or may be used for the diagnosis of tuberculosis.</p>																																											
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Description

5

COMPOUNDS AND METHODS FOR IMMUNOTHERAPY
AND DIAGNOSIS OF TUBERCULOSISTechnical Field

10 The present invention relates generally to detecting, treating and preventing *Mycobacterium tuberculosis* infection. The invention is more particularly related to polypeptides comprising a *Mycobacterium tuberculosis* antigen, or a portion or other variant thereof, and the use of such polypeptides for diagnosing and vaccinating against *Mycobacterium tuberculosis* infection.

15

Background of the Invention

20 Tuberculosis is a chronic, infectious disease, that is generally caused by infection with *Mycobacterium tuberculosis*. It is a major disease in developing countries, as well as an increasing problem in developed areas of the world, with about 8 million new cases and 3 million deaths each year. Although the infection may be asymptomatic for a considerable period of time, the disease is most commonly manifested as an acute inflammation of the lungs, resulting in fever and a nonproductive cough. If left untreated, serious complications and death typically result.

25 Although tuberculosis can generally be controlled using extended antibiotic therapy, such treatment is not sufficient to prevent the spread of the disease. Infected individuals may be asymptomatic, but contagious, for some time. In addition,

although compliance with the treatment regimen is critical, patient behavior is difficult to monitor. Some patients do not complete the course of treatment, which can lead to ineffective treatment and the development of drug resistance.

Inhibiting the spread of tuberculosis requires effective vaccination and accurate, early diagnosis of the disease. Currently, vaccination with live bacteria is the most efficient method for inducing protective immunity. The most common Mycobacterium employed for this purpose is *Bacillus Calmette-Guerin* (BCG), an avirulent strain of *Mycobacterium bovis*. However, the safety and efficacy of BCG is a source of controversy and some countries, such as the United States, do not vaccinate the general public. Diagnosis is commonly achieved using a skin test, which involves intradermal exposure to tuberculin PPD (protein-purified derivative). Antigen-specific T cell responses result in measurable induration at the injection site by 48-72 hours after injection, which indicates exposure to Mycobacterial antigens. Sensitivity and specificity have, however, been a problem with this test, and individuals vaccinated with BCG cannot be distinguished from infected individuals.

While macrophages have been shown to act as the principal effectors of *M. tuberculosis* immunity, T cells are the predominant inducers of such immunity. The essential role of T cells in protection against *M. tuberculosis* infection is illustrated by the frequent occurrence of *M. tuberculosis* in AIDS patients, due to the depletion of CD4 T cells associated with human immunodeficiency virus (HIV) infection. Mycobacterium-reactive CD4 T cells have been shown to be potent producers of gamma-interferon (IFN- γ), which, in turn, has been shown to trigger the anti-mycobacterial effects of macrophages in mice. While the role of IFN- γ in humans is less clear, studies have shown that 1,25-dihydroxy-vitamin D3, either alone or in combination with IFN- γ or tumor necrosis factor-alpha, activates human macrophages to inhibit *M. tuberculosis* infection. Furthermore, it is known that IFN- γ stimulates human macrophages to make 1,25-dihydroxy-vitamin D3. Similarly, IL-12 has been shown to play a role in stimulating resistance to *M. tuberculosis* infection. For a review of the immunology of *M. tuberculosis* infection see Chan and Kaufmann in

Tuberculosis: Pathogenesis, Protection and Control, Bloom (ed.), ASM Press, Washington, DC, 1994.

Accordingly, there is a need in the art for improved vaccines and methods for preventing, treating and detecting tuberculosis. The present invention 5 fulfills these needs and further provides other related advantages.

Summary of the Invention

Briefly stated, this invention provides compounds and methods for preventing and diagnosing tuberculosis. In one aspect, polypeptides are provided 10 comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications. In one embodiment of this aspect, the soluble antigen has one of the following N-terminal sequences:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-
15 Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-
Ser; (SEQ ID No. 121)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-
Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- 20 (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-
Pro; (SEQ ID No. 123)
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val;
(SEQ ID No. 124)
- 25 (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID
No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-
Pro-Pro-Ser; (SEQ ID No. 126)
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-
Gly; (SEQ ID No. 127)

- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128)
- 5 (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) or
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)

10 wherein Xaa may be any amino acid.

In a related aspect, polypeptides are provided comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, the antigen having one of the following N-terminal sequences:

- 15 (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 137) or
- (n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129)

wherein Xaa may be any amino acid.

20 In another embodiment, the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101 or a complement thereof under moderately stringent
25 conditions.

In a related aspect, the polypeptides comprise an immunogenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, wherein the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 26-51, the complements of said sequences, and

DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 26-51 or a complement thereof under moderately stringent conditions.

In related aspects, DNA sequences encoding the above polypeptides, expression vectors comprising these DNA sequences and host cells transformed or
5 transfected with such expression vectors are also provided.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known *M. tuberculosis* antigen.

Within other aspects, the present invention provides pharmaceutical
10 compositions that comprise one or more of the above polypeptides, or a DNA molecule encoding such polypeptides, and a physiologically acceptable carrier. The invention also provides vaccines comprising one or more of the polypeptides as described above and a non-specific immune response enhancer, together with vaccines comprising one or more DNA sequences encoding such polypeptides and a non-specific immune
15 response enhancer.

In yet another aspect, methods are provided for inducing protective immunity in a patient, comprising administering to a patient an effective amount of one or more of the above polypeptides.

In further aspects of this invention, methods and diagnostic kits are
20 provided for detecting tuberculosis in a patient. The methods comprise contacting dermal cells of a patient with one or more of the above polypeptides and detecting an immune response on the patient's skin. The diagnostic kits comprise one or more of the above polypeptides in combination with an apparatus sufficient to contact the polypeptide with the dermal cells of a patient.

25 These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

Brief Description of the Drawings and Sequence Identifiers

Figure 1A and B illustrate the stimulation of proliferation and interferon- γ production in T cells derived from a first and a second *M. tuberculosis*-immune donor, respectively, by the 14 Kd, 20 Kd and 26 Kd antigens described in Example 1.

5 Figure 2 illustrates the stimulation of proliferation and interferon- γ production in T cells derived from an *M. tuberculosis*-immune individual by the two representative polypeptides TbRa3 and TbRa9.

- 10 SEQ. ID NO. 1 is the DNA sequence of TbRa1.
SEQ. ID NO. 2 is the DNA sequence of TbRa10.
SEQ. ID NO. 3 is the DNA sequence of TbRa11.
SEQ. ID NO. 4 is the DNA sequence of TbRa12.
SEQ. ID NO. 5 is the DNA sequence of TbRa13.
SEQ. ID NO. 6 is the DNA sequence of TbRa16.
15 SEQ. ID NO. 7 is the DNA sequence of TbRa17.
SEQ. ID NO. 8 is the DNA sequence of TbRa18.
SEQ. ID NO. 9 is the DNA sequence of TbRa19.
SEQ. ID NO. 10 is the DNA sequence of TbRa24.
SEQ. ID NO. 11 is the DNA sequence of TbRa26.
20 SEQ. ID NO. 12 is the DNA sequence of TbRa28.
SEQ. ID NO. 13 is the DNA sequence of TbRa29.
SEQ. ID NO. 14 is the DNA sequence of TbRa2A.
SEQ. ID NO. 15 is the DNA sequence of TbRa3.
SEQ. ID NO. 16 is the DNA sequence of TbRa32.
25 SEQ. ID NO. 17 is the DNA sequence of TbRa35.
SEQ. ID NO. 18 is the DNA sequence of TbRa36.
SEQ. ID NO. 19 is the DNA sequence of TbRa4.
SEQ. ID NO. 20 is the DNA sequence of TbRa9.
SEQ. ID NO. 21 is the DNA sequence of TbRaB.
30 SEQ. ID NO. 22 is the DNA sequence of TbRaC.

- SEQ. ID NO. 23 is the DNA sequence of TbRaD.
- SEQ. ID NO. 24 is the DNA sequence of YYWCPG.
- SEQ. ID NO. 25 is the DNA sequence of AAMK.
- SEQ. ID NO. 26 is the DNA sequence of TbL-23.
- 5 SEQ. ID NO. 27 is the DNA sequence of TbL-24.
- SEQ. ID NO. 28 is the DNA sequence of TbL-25.
- SEQ. ID NO. 29 is the DNA sequence of TbL-28.
- SEQ. ID NO. 30 is the DNA sequence of TbL-29.
- SEQ. ID NO. 31 is the DNA sequence of TbH-5.
- 10 SEQ. ID NO. 32 is the DNA sequence of TbH-8.
- SEQ. ID NO. 33 is the DNA sequence of TbH-9.
- SEQ. ID NO. 34 is the DNA sequence of TbM-1.
- SEQ. ID NO. 35 is the DNA sequence of TbM-3.
- SEQ. ID NO. 36 is the DNA sequence of TbM-6.
- 15 SEQ. ID NO. 37 is the DNA sequence of TbM-7.
- SEQ. ID NO. 38 is the DNA sequence of TbM-9.
- SEQ. ID NO. 39 is the DNA sequence of TbM-12.
- SEQ. ID NO. 40 is the DNA sequence of TbM-13.
- SEQ. ID NO. 41 is the DNA sequence of TbM-14.
- 20 SEQ. ID NO. 42 is the DNA sequence of TbM-15.
- SEQ. ID NO. 43 is the DNA sequence of TbH-4.
- SEQ. ID NO. 44 is the DNA sequence of TbH-4-FWD.
- SEQ. ID NO. 45 is the DNA sequence of TbH-12.
- SEQ. ID NO. 46 is the DNA sequence of Tb38-1.
- 25 SEQ. ID NO. 47 is the DNA sequence of Tb38-4.
- SEQ. ID NO. 48 is the DNA sequence of TbL-17.
- SEQ. ID NO. 49 is the DNA sequence of TbL-20.
- SEQ. ID NO. 50 is the DNA sequence of TbL-21.
- SEQ. ID NO. 51 is the DNA sequence of TbH-16.
- 30 SEQ. ID NO. 52 is the DNA sequence of DPEP.

- SEQ. ID NO. 53 is the deduced amino acid sequence of DPEP.
- SEQ. ID NO. 54 is the protein sequence of DPV N-terminal Antigen.
- SEQ. ID NO. 55 is the protein sequence of AVGS N-terminal Antigen.
- SEQ. ID NO. 56 is the protein sequence of AAMK N-terminal Antigen.
- 5 SEQ. ID NO. 57 is the protein sequence of YYWC N-terminal Antigen.
- SEQ. ID NO. 58 is the protein sequence of DIGS N-terminal Antigen.
- SEQ. ID NO. 59 is the protein sequence of AEES N-terminal Antigen.
- SEQ. ID NO. 60 is the protein sequence of DPEP N-terminal Antigen.
- SEQ. ID NO. 61 is the protein sequence of APKT N-terminal Antigen.
- 10 SEQ. ID NO. 62 is the protein sequence of DPAS N-terminal Antigen.
- SEQ. ID NO. 63 is the deduced amino acid sequence of TbRa1.
- SEQ. ID NO. 64 is the deduced amino acid sequence of TbRa10.
- SEQ. ID NO. 65 is the deduced amino acid sequence of TbRa11.
- SEQ. ID NO. 66 is the deduced amino acid sequence of TbRa12.
- 15 SEQ. ID NO. 67 is the deduced amino acid sequence of TbRa13.
- SEQ. ID NO. 68 is the deduced amino acid sequence of TbRa16.
- SEQ. ID NO. 69 is the deduced amino acid sequence of TbRa17.
- SEQ. ID NO. 70 is the deduced amino acid sequence of TbRa18.
- SEQ. ID NO. 71 is the deduced amino acid sequence of TbRa19.
- 20 SEQ. ID NO. 72 is the deduced amino acid sequence of TbRa24.
- SEQ. ID NO. 73 is the deduced amino acid sequence of TbRa26.
- SEQ. ID NO. 74 is the deduced amino acid sequence of TbRa28.
- SEQ. ID NO. 75 is the deduced amino acid sequence of TbRa29.
- SEQ. ID NO. 76 is the deduced amino acid sequence of TbRa2A.
- 25 SEQ. ID NO. 77 is the deduced amino acid sequence of TbRa3.
- SEQ. ID NO. 78 is the deduced amino acid sequence of TbRa32.
- SEQ. ID NO. 79 is the deduced amino acid sequence of TbRa35.
- SEQ. ID NO. 80 is the deduced amino acid sequence of TbRa36.
- SEQ. ID NO. 81 is the deduced amino acid sequence of TbRa4.
- 30 SEQ. ID NO. 82 is the deduced amino acid sequence of TbRa9.

- SEQ. ID NO. 83 is the deduced amino acid sequence of TbRaB.
- SEQ. ID NO. 84 is the deduced amino acid sequence of TbRaC.
- SEQ. ID NO. 85 is the deduced amino acid sequence of TbRaD.
- SEQ. ID NO. 86 is the deduced amino acid sequence of YYWCPG.
- 5 SEQ. ID NO. 87 is the deduced amino acid sequence of TbAAMK.
- SEQ. ID NO. 88 is the deduced amino acid sequence of Tb38-1.
- SEQ. ID NO. 89 is the deduced amino acid sequence of TbH-4.
- SEQ. ID NO. 90 is the deduced amino acid sequence of TbH-8.
- SEQ. ID NO. 91 is the deduced amino acid sequence of TbH-9.
- 10 SEQ. ID NO. 92 is the deduced amino acid sequence of TbH-12.
- SEQ. ID NO. 93 is the amino acid sequence of Tb38-1 Peptide 1.
- SEQ. ID NO. 94 is the amino acid sequence of Tb38-1 Peptide 2.
- SEQ. ID NO. 95 is the amino acid sequence of Tb38-1 Peptide 3.
- SEQ. ID NO. 96 is the amino acid sequence of Tb38-1 Peptide 4.
- 15 SEQ. ID NO. 97 is the amino acid sequence of Tb38-1 Peptide 5.
- SEQ. ID NO. 98 is the amino acid sequence of Tb38-1 Peptide 6.
- SEQ. ID NO. 99 is the DNA sequence of DPAS.
- SEQ. ID NO. 100 is the deduced amino acid sequence of DPAS.
- SEQ. ID NO. 101 is the DNA sequence of DPV.
- 20 SEQ. ID NO. 102 is the deduced amino acid sequence of DPV.
- SEQ. ID NO. 103 is the DNA sequence of ESAT-6.
- SEQ. ID NO. 104 is the deduced amino acid sequence of ESAT-6.
- SEQ. ID NO. 105 is the DNA sequence of TbH-8-2.
- SEQ. ID NO. 106 is the DNA sequence of TbH-9FL.
- 25 SEQ. ID NO. 107 is the deduced amino acid sequence of TbH-9FL.
- SEQ. ID NO. 108 is the DNA sequence of TbH-9-1.
- SEQ. ID NO. 109 is the deduced amino acid sequence of TbH-9-1.
- SEQ. ID NO. 110 is the DNA sequence of TbH-9-4.
- SEQ. ID NO. 111 is the deduced amino acid sequence of TbH-9-4.
- 30 SEQ. ID NO. 112 is the DNA sequence of Tb38-1F2 IN.

- SEQ. ID NO. 113 is the DNA sequence of Tb38-2F2 RP.
- SEQ. ID NO. 114 is the deduced amino acid sequence of Tb37-FL.
- SEQ. ID NO. 115 is the deduced amino acid sequence of Tb38-IN.
- SEQ. ID NO. 116 is the DNA sequence of Tb38-1F3.
- 5 SEQ. ID NO. 117 is the deduced amino acid sequence of Tb38-1F3.
- SEQ. ID NO. 118 is the DNA sequence of Tb38-1F5.
- SEQ. ID NO. 119 is the DNA sequence of Tb38-1F6.
- SEQ. ID NO. 120 is the deduced N-terminal amino acid sequence of DPV.
- SEQ. ID NO. 121 is the deduced N-terminal amino acid sequence of AVGS.
- 10 SEQ. ID NO. 122 is the deduced N-terminal amino acid sequence of AAMK.
- SEQ. ID NO. 123 is the deduced N-terminal amino acid sequence of YYWC.
- SEQ. ID NO. 124 is the deduced N-terminal amino acid sequence of DIGS.
- SEQ. ID NO. 125 is the deduced N-terminal amino acid sequence of AEES.
- SEQ. ID NO. 126 is the deduced N-terminal amino acid sequence of DPEP.
- 15 SEQ. ID NO. 127 is the deduced N-terminal amino acid sequence of APKT.
- SEQ. ID NO. 128 is the deduced amino acid sequence of DPAS.
- SEQ. ID NO. 129 is the protein sequence of DPPD N-terminal Antigen.
- SEQ ID NO. 130-133 are the protein sequences of four DPPD cyanogen bromide fragments.
- 20 SEQ ID NO. 134 is the N-terminal protein sequence of XDS antigen.
- SEQ ID NO. 135 is the N-terminal protein sequence of AGD antigen.
- SEQ ID NO. 136 is the N-terminal protein sequence of APE antigen.
- SEQ ID NO. 137 is the N-terminal protein sequence of XYI antigen.

25 Detailed Description of the Invention

As noted above, the present invention is generally directed to compositions and methods for preventing, treating and diagnosing tuberculosis. The compositions of the subject invention include polypeptides that comprise at least one immunogenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that 30 differs only in conservative substitutions and/or modifications. Polypeptides within the scope of the present invention include, but are not limited to, immunogenic soluble

M. tuberculosis antigens. A "soluble *M. tuberculosis* antigen" is a protein of *M. tuberculosis* origin that is present in *M. tuberculosis* culture filtrate. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins (*i.e.*, antigens), wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising an immunogenic portion of one of the above antigens may consist entirely of the immunogenic portion, or may contain additional sequences. The additional sequences may be derived from the native *M. tuberculosis* antigen or may be heterologous, and such sequences may (but need not) be immunogenic.

10 "Immunogenic," as used herein, refers to the ability to elicit an immune response (*e.g.*, cellular) in a patient, such as a human, and/or in a biological sample. In particular, antigens that are immunogenic (and immunogenic portions or other variants of such antigens) are capable of stimulating cell proliferation, interleukin-12 production and/or interferon- γ production in biological samples comprising one or more cells selected from the group of T cells, NK cells, B cells and macrophages, where the cells are derived from an *M. tuberculosis*-immune individual. Polypeptides comprising at least an immunogenic portion of one or more *M. tuberculosis* antigens may generally be used to detect tuberculosis or to induce protective immunity against tuberculosis in a patient.

15 The compositions and methods of this invention also encompass variants of the above polypeptides. A "variant," as used herein, is a polypeptide that differs from the native antigen only in conservative substitutions and/or modifications, such that the ability of the polypeptide to induce an immune response is retained. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the immunogenic properties of the modified polypeptide using, for example, the representative procedures described herein.

20 A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. In general, the following

groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also (or alternatively) be modified by, for example, the
5 deletion or addition of amino acids that have minimal influence on the immunogenic properties, secondary structure and hydrophobic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease
10 of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

In a related aspect, combination polypeptides are disclosed. A "combination polypeptide" is a polypeptide comprising at least one of the above
15 immunogenic portions and one or more additional immunogenic *M. tuberculosis* sequences, which are joined via a peptide linkage into a single amino acid chain. The sequences may be joined directly (*i.e.*, with no intervening amino acids) or may be joined by way of a linker sequence (*e.g.*, Gly-Cys-Gly) that does not significantly diminish the immunogenic properties of the component polypeptides.

20 In general, *M. tuberculosis* antigens, and DNA sequences encoding such antigens, may be prepared using any of a variety of procedures. For example, soluble antigens may be isolated from *M. tuberculosis* culture filtrate by procedures known to those of ordinary skill in the art, including anion-exchange and reverse phase chromatography. Purified antigens are then evaluated for their ability to elicit an
25 appropriate immune response (*e.g.*, cellular) using, for example, the representative methods described herein. Immunogenic antigens may then be partially sequenced using techniques such as traditional Edman chemistry. See Edman and Berg, *Eur. J. Biochem.* 80:116-132, 1967.

Immunogenic antigens may also be produced recombinantly using a
30 DNA sequence that encodes the antigen, which has been inserted into an expression

- vector and expressed in an appropriate host. DNA molecules encoding soluble antigens may be isolated by screening an appropriate *M. tuberculosis* expression library with anti-sera (*e.g.*, rabbit) raised specifically against soluble *M. tuberculosis* antigens. DNA sequences encoding antigens that may or may not be soluble may be identified by
- 5 screening an appropriate *M. tuberculosis* genomic or cDNA expression library with sera obtained from patients infected with *M. tuberculosis*. Such screens may generally be performed using techniques well known to those of ordinary skill in the art, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989.
- 10 DNA sequences encoding soluble antigens may also be obtained by screening an appropriate *M. tuberculosis* cDNA or genomic DNA library for DNA sequences that hybridize to degenerate oligonucleotides derived from partial amino acid sequences of isolated soluble antigens. Degenerate oligonucleotide sequences for use in such a screen may be designed and synthesized, and the screen may be performed, as
- 15 described (for example) in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989 (and references cited therein). Polymerase chain reaction (PCR) may also be employed, using the above oligonucleotides in methods well known in the art, to isolate a nucleic acid probe from a cDNA or genomic library. The library screen may then be performed using the isolated
- 20 probe.

Alternatively, genomic or cDNA libraries derived from *M. tuberculosis* may be screened directly using peripheral blood mononuclear cells (PBMCs) or T cell lines or clones derived from one or more *M. tuberculosis*-immune individuals. In general, PBMCs and/or T cells for use in such screens may be prepared as described

25 below. Direct library screens may generally be performed by assaying pools of expressed recombinant proteins for the ability to induce proliferation and/or interferon- γ production in T cells derived from an *M. tuberculosis*-immune individual. Alternatively, potential T cell antigens may be first selected based on antibody reactivity, as described above.

Regardless of the method of preparation, the antigens (and immunogenic portions thereof) described herein (which may or may not be soluble) have the ability to induce an immunogenic response. More specifically, the antigens have the ability to induce proliferation and/or cytokine production (*i.e.*, interferon- γ and/or interleukin-12 production) in T cells, NK cells, B cells and/or macrophages derived from an *M. tuberculosis*-immune individual. The selection of cell type for use in evaluating an immunogenic response to a antigen will, of course, depend on the desired response. For example, interleukin-12 production is most readily evaluated using preparations containing B cells and/or macrophages. An *M. tuberculosis*-immune individual is one who is considered to be resistant to the development of tuberculosis by virtue of having mounted an effective T cell response to *M. tuberculosis* (*i.e.*, substantially free of disease symptoms). Such individuals may be identified based on a strongly positive (*i.e.*, greater than about 10 mm diameter induration) intradermal skin test response to tuberculosis proteins (PPD) and an absence of any signs or symptoms of tuberculosis disease. T cells, NK cells, B cells and macrophages derived from *M. tuberculosis*-immune individuals may be prepared using methods known to those of ordinary skill in the art. For example, a preparation of PBMCs (*i.e.*, peripheral blood mononuclear cells) may be employed without further separation of component cells. PBMCs may generally be prepared, for example, using density centrifugation through Ficoll™ (Winthrop Laboratories, NY). T cells for use in the assays described herein may also be purified directly from PBMCs. Alternatively, an enriched T cell line reactive against mycobacterial proteins, or T cell clones reactive to individual mycobacterial proteins, may be employed. Such T cell clones may be generated by, for example, culturing PBMCs from *M. tuberculosis*-immune individuals with mycobacterial proteins for a period of 2-4 weeks. This allows expansion of only the mycobacterial protein-specific T cells, resulting in a line composed solely of such cells. These cells may then be cloned and tested with individual proteins, using methods known to those of ordinary skill in the art, to more accurately define individual T cell specificity. In general, antigens that test positive in assays for proliferation and/or cytokine production (*i.e.*, interferon- γ and/or interleukin-12 production) performed using T cells, NK cells, B cells

and/or macrophages derived from an *M. tuberculosis*-immune individual are considered immunogenic. Such assays may be performed, for example, using the representative procedures described below. Immunogenic portions of such antigens may be identified using similar assays, and may be present within the polypeptides described herein.

5 The ability of a polypeptide (*e.g.*, an immunogenic antigen, or a portion or other variant thereof) to induce cell proliferation is evaluated by contacting the cells (*e.g.*, T cells and/or NK cells) with the polypeptide and measuring the proliferation of the cells. In general, the amount of polypeptide that is sufficient for evaluation of about 10^5 cells ranges from about 10 ng/mL to about 100 μ g/mL and preferably is about
10 10 μ g/mL. The incubation of polypeptide with cells is typically performed at 37°C for about six days. Following incubation with polypeptide, the cells are assayed for a proliferative response, which may be evaluated by methods known to those of ordinary skill in the art, such as exposing cells to a pulse of radiolabeled thymidine and measuring the incorporation of label into cellular DNA. In general, a polypeptide that
15 results in at least a three fold increase in proliferation above background (*i.e.*, the proliferation observed for cells cultured without polypeptide) is considered to be able to induce proliferation.

20 The ability of a polypeptide to stimulate the production of interferon- γ and/or interleukin-12 in cells may be evaluated by contacting the cells with the polypeptide and measuring the level of interferon- γ or interleukin-12 produced by the cells. In general, the amount of polypeptide that is sufficient for the evaluation of about 10^5 cells ranges from about 10 ng/mL to about 100 μ g/mL and preferably is about 10 μ g/mL. The polypeptide may, but need not, be immobilized on a solid support, such as a bead or a biodegradable microsphere, such as those described in U.S. Patent
25 Nos. 4,897,268 and 5,075,109. The incubation of polypeptide with the cells is typically performed at 37°C for about six days. Following incubation with polypeptide, the cells are assayed for interferon- γ and/or interleukin-12 (or one or more subunits thereof), which may be evaluated by methods known to those of ordinary skill in the art, such as an enzyme-linked immunosorbent assay (ELISA) or, in the case of IL-12 P70 subunit, a
30 bioassay such as an assay measuring proliferation of T cells. In general, a polypeptide

that results in the production of at least 50 pg of interferon- γ per mL of cultured supernatant (containing 10^4 - 10^5 T cells per mL) is considered able to stimulate the production of interferon- γ . A polypeptide that stimulates the production of at least 10 pg/mL of IL-12 P70 subunit, and/or at least 100 pg/mL of IL-12 P40 subunit, per 10^5 5 macrophages or B cells (or per 3×10^5 PBMC) is considered able to stimulate the production of IL-12.

In general, immunogenic antigens are those antigens that stimulate proliferation and/or cytokine production (*i.e.*, interferon- γ and/or interleukin-12 production) in T cells, NK cells, B cells and/or macrophages derived from at least about 10 25% of *M. tuberculosis*-immune individuals. Among these immunogenic antigens, polypeptides having superior therapeutic properties may be distinguished based on the magnitude of the responses in the above assays and based on the percentage of individuals for which a response is observed. In addition, antigens having superior therapeutic properties will not stimulate proliferation and/or cytokine production *in* 15 *vitro* in cells derived from more than about 25% of individuals that are not *M. tuberculosis*-immune, thereby eliminating responses that are not specifically due to *M. tuberculosis*-responsive cells. Those antigens that induce a response in a high percentage of T cell, NK cell, B cell and/or macrophage preparations from *M. tuberculosis*-immune individuals (with a low incidence of responses in cell 20 preparations from other individuals) have superior therapeutic properties.

Antigens with superior therapeutic properties may also be identified based on their ability to diminish the severity of *M. tuberculosis* infection in experimental animals, when administered as a vaccine. Suitable vaccine preparations for use on experimental animals are described in detail below. Efficacy may be 25 determined based on the ability of the antigen to provide at least about a 50% reduction in bacterial numbers and/or at least about a 40% decrease in mortality following experimental infection. Suitable experimental animals include mice, guinea pigs and primates.

Antigens having superior diagnostic properties may generally be 30 identified based on the ability to elicit a response in an intradermal skin test performed

on an individual with active tuberculosis, but not in a test performed on an individual who is not infected with *M. tuberculosis*. Skin tests may generally be performed as described below, with a response of at least 5 mm induration considered positive.

Immunogenic portions of the antigens described herein may be prepared 5 and identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3d ed., Raven Press, 1993, pp. 243-247 and references cited therein. Such techniques include screening polypeptide portions of the native antigen for immunogenic properties. The representative proliferation and cytokine production assays described herein may generally be employed in these screens. An immunogenic 10 portion of a polypeptide is a portion that, within such representative assays, generates an immune response (*e.g.*, proliferation, interferon- γ production and/or interleukin-12 production) that is substantially similar to that generated by the full length antigen. In other words, an immunogenic portion of an antigen may generate at least about 20%, and preferably about 100%, of the proliferation induced by the full length antigen in the 15 model proliferation assay described herein. An immunogenic portion may also, or alternatively, stimulate the production of at least about 20%, and preferably about 100%, of the interferon- γ and/or interleukin-12 induced by the full length antigen in the model assay described herein.

Portions and other variants of *M. tuberculosis* antigens may be generated 20 by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are 25 sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc., Foster City, CA, and may be operated according to the manufacturer's instructions. Variants of a native antigen may generally be prepared using standard mutagenesis techniques, such 30 as oligonucleotide-directed site-specific mutagenesis. Sections of the DNA sequence

may also be removed using standard techniques to permit preparation of truncated polypeptides.

Recombinant polypeptides containing portions and/or variants of a native antigen may be readily prepared from a DNA sequence encoding the polypeptide 5 using a variety of techniques well known to those of ordinary skill in the art. For example, supernatants from suitable host/vector systems which secrete recombinant protein into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or 10 more reverse phase HPLC steps can be employed to further purify a recombinant protein.

Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or 15 transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. The DNA sequences expressed in this manner may encode naturally occurring antigens, portions of naturally occurring antigens, or other 20 variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in substantially pure form. Preferably, the polypeptides are at least about 80% pure, more preferably at least about 90% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in 25 detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

In certain specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a soluble *M. tuberculosis* antigen having one of the following N-terminal sequences, or a variant thereof that 30 differs only in conservative substitutions and/or modifications:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 121)
- 5 (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 123)
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val; (SEQ ID No. 124)
- 10 (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Ala-Ala-Ala-Ser-Pro-Pro-Ser; (SEQ ID No. 126)
- 15 (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly; (SEQ ID No. 127)
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128)
- 20 (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) or
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)

25 wherein Xaa may be any amino acid, preferably a cysteine residue. A DNA sequence encoding the antigen identified as (g) above is provided in SEQ ID No. 52, and the polypeptide encoded by SEQ ID No. 52 is provided in SEQ ID No. 53. A DNA sequence encoding the antigen defined as (a) above is provided in SEQ ID No. 101; its deduced amino acid sequence is provided in SEQ ID No. 102. A DNA sequence

corresponding to antigen (d) above is provided in SEQ ID No. 24 a DNA sequence corresponding to antigen (c) is provided in SEQ ID No. 25 and a DNA sequence corresponding to antigen (i) is provided in SEQ ID No. 99; its deduced amino acid sequence is provided in SEQ ID No. 100.

5 In a further specific embodiment, the subject invention discloses polypeptides comprising at least an immunogenic portion of an *M. tuberculosis* antigen having one of the following N-terminal sequences, or a variant thereof that differs only in conservative substitutions and/or modifications:

- 10 (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No 137) or
(n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129)

wherein Xaa may be any amino acid, preferably a cysteine residue.

15 In other specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a soluble *M. tuberculosis* antigen (or a variant of such an antigen) that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos.: 1, 2, 4-10, 13-25 and 52; (b) the complements of such DNA sequences, or (c) DNA sequences substantially homologous to a sequence in (a) or (b).

20 In further specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a *M. tuberculosis* antigen (or a variant of such an antigen), which may or may not be soluble, that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos.: 26-51, (b) the complements of such DNA sequences or (c) DNA sequences 25 substantially homologous to a sequence in (a) or (b).

30 In the specific embodiments discussed above, the *M. tuberculosis* antigens include variants that are encoded by DNA sequences which are substantially homologous to one or more of DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include

prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the case of cross-species homology at 45°C, 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also 5 within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of 10 the present invention and a known *M. tuberculosis* antigen, such as the 38 kD antigen described above or ESAT-6 (SEQ ID Nos. 103 and 104), together with variants of such fusion proteins. The fusion proteins of the present invention may also include a linker peptide between the first and second polypeptides.

A DNA sequence encoding a fusion protein of the present invention is 15 constructed using known recombinant DNA techniques to assemble separate DNA sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a DNA sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA 20 translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into 25 the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide 30 functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser

residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent 5 No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable 10 transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

15 In another aspect, the present invention provides methods for using one or more of the above polypeptides or fusion proteins (or DNA molecules encoding such polypeptides) to induce protective immunity against tuberculosis in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with a disease, or may be free of detectable disease and/or infection. In 20 other words, protective immunity may be induced to prevent or treat tuberculosis.

In this aspect, the polypeptide, fusion protein or DNA molecule is generally present within a pharmaceutical composition and/or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a 25 physiologically acceptable carrier. Vaccines may comprise one or more of the above polypeptides and a non-specific immune response enhancer, such as an adjuvant or a liposome (into which the polypeptide is incorporated). Such pharmaceutical compositions and vaccines may also contain other *M. tuberculosis* antigens, either incorporated into a combination polypeptide or present within a separate polypeptide.

Alternatively, a vaccine may contain DNA encoding one or more polypeptides as described above, such that the polypeptide is generated *in situ*. In such vaccines, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacterial and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

In a related aspect, a DNA vaccine as described above may be administered simultaneously with or sequentially to either a polypeptide of the present invention or a known *M. tuberculosis* antigen, such as the 38 kD antigen described above. For example, administration of DNA encoding a polypeptide of the present invention, either "naked" or in a delivery system as described above, may be followed by administration of an antigen in order to enhance the protective immune effect of the vaccine.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunization using BCG. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Between 1 and 3 doses may be administered for a 1-36 week period. Preferably, 3 doses are administered, at

- intervals of 3-4 months, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or DNA that, when administered as described above, is capable of raising an immune response in an immunized patient sufficient to protect the patient
- 5 from *M. tuberculosis* infection for at least 1-2 years. In general, the amount of polypeptide present in a dose (or produced *in situ* by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 µg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.
- 10 While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier,
- 15 such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactic galactide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.
- 20 Any of a variety of adjuvants may be employed in the vaccines of this invention to nonspecifically enhance the immune response. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis*. Suitable adjuvants are
- 25 commercially available as, for example, Freund's Incomplete Adjuvant and Freund's Complete Adjuvant (Difco Laboratories) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ). Other suitable adjuvants include alum, biodegradable microspheres, monophosphoryl lipid A and quil A.

In another aspect, this invention provides methods for using one or more

30 of the polypeptides described above to diagnose tuberculosis using a skin test. As used

herein, a "skin test" is any assay performed directly on a patient in which a delayed-type hypersensitivity (DTH) reaction (such as swelling, reddening or dermatitis) is measured following intradermal injection of one or more polypeptides as described above. Such injection may be achieved using any suitable device sufficient to contact the 5 polypeptide or polypeptides with dermal cells of the patient, such as a tuberculin syringe or 1 mL syringe. Preferably, the reaction is measured at least 48 hours after injection, more preferably 48-72 hours.

The DTH reaction is a cell-mediated immune response, which is greater in patients that have been exposed previously to the test antigen (*i.e.*, the immunogenic 10 portion of the polypeptide employed, or a variant thereof). The response may be measured visually, using a ruler. In general, a response that is greater than about 0.5 cm in diameter, preferably greater than about 1.0 cm in diameter, is a positive response, indicative of tuberculosis infection, which may or may not be manifested as an active disease.

15 The polypeptides of this invention are preferably formulated, for use in a skin test, as pharmaceutical compositions containing a polypeptide and a physiologically acceptable carrier, as described above. Such compositions typically contain one or more of the above polypeptides in an amount ranging from about 1 μ g to about 100 μ g, preferably from about 10 μ g to about 50 μ g in a volume of 0.1 mL. 20 Preferably, the carrier employed in such pharmaceutical compositions is a saline solution with appropriate preservatives, such as phenol and/or Tween 80TM.

In a preferred embodiment, a polypeptide employed in a skin test is of sufficient size such that it remains at the site of injection for the duration of the reaction period. In general, a polypeptide that is at least 9 amino acids in length is sufficient. 25 The polypeptide is also preferably broken down by macrophages within hours of injection to allow presentation to T-cells. Such polypeptides may contain repeats of one or more of the above sequences and/or other immunogenic or nonimmunogenic sequences.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

5

EXAMPLE 1

PURIFICATION AND CHARACTERIZATION OF POLYPEPTIDES FROM *M. TUBERCULOSIS* CULTURE FILTRATE

10 This example illustrates the preparation of *M. tuberculosis* soluble polypeptides from culture filtrate. Unless otherwise noted, all percentages in the following example are weight per volume.

15 *M. tuberculosis* (either H37Ra, ATCC No. 25177, or H37Rv, ATCC No. 25618) was cultured in sterile GAS media at 37°C for fourteen days. The media was then vacuum filtered (leaving the bulk of the cells) through a 0.45 µ filter into a sterile 2.5 L bottle. The media was next filtered through a 0.2 µ filter into a sterile 4 L bottle and NaN₃ was added to the culture filtrate to a concentration of 0.04%. The bottles were then placed in a 4°C cold room.

20 The culture filtrate was concentrated by placing the filtrate in a 12 L reservoir that had been autoclaved and feeding the filtrate into a 400 ml Amicon stir cell which had been rinsed with ethanol and contained a 10,000 kDa MWCO membrane. The pressure was maintained at 60 psi using nitrogen gas. This procedure reduced the 12 L volume to approximately 50 ml.

25 The culture filtrate was dialyzed into 0.1% ammonium bicarbonate using a 8,000 kDa MWCO cellulose ester membrane, with two changes of ammonium bicarbonate solution. Protein concentration was then determined by a commercially available BCA assay (Pierce, Rockford, IL).

30 The dialyzed culture filtrate was then lyophilized, and the polypeptides resuspended in distilled water. The polypeptides were dialyzed against 0.01 mM 1,3 bis[tris(hydroxymethyl)-methylamino]propane, pH 7.5 (Bis-Tris propane buffer), the

initial conditions for anion exchange chromatography. Fractionation was performed using gel profusion chromatography on a POROS 146 II Q/M anion exchange column 4.6 mm x 100 mm (Perseptive BioSystems, Framingham, MA) equilibrated in 0.01 mM Bis-Tris propane buffer pH 7.5. Polypeptides were eluted with a linear 0-0.5 M NaCl gradient in the above buffer system. The column eluent was monitored at a wavelength of 220 nm.

The pools of polypeptides eluting from the ion exchange column were dialyzed against distilled water and lyophilized. The resulting material was dissolved in 0.1% trifluoroacetic acid (TFA) pH 1.9 in water, and the polypeptides were purified on 10 a Delta-Pak C18 column (Waters, Milford, MA) 300 Angstrom pore size, 5 micron particle size (3.9 x 150 mm). The polypeptides were eluted from the column with a linear gradient from 0-60% dilution buffer (0.1% TFA in acetonitrile). The flow rate was 0.75 ml/minute and the HPLC eluent was monitored at 214 nm. Fractions containing the eluted polypeptides were collected to maximize the purity of the 15 individual samples. Approximately 200 purified polypeptides were obtained.

The purified polypeptides were then screened for the ability to induce T-cell proliferation in PBMC preparations. The PBMCs from donors known to be PPD skin test positive and whose T-cells were shown to proliferate in response to PPD and crude soluble proteins from MTB were cultured in medium comprising RPMI 1640 20 supplemented with 10% pooled human serum and 50 µg/ml gentamicin. Purified polypeptides were added in duplicate at concentrations of 0.5 to 10 µg/mL. After six days of culture in 96-well round-bottom plates in a volume of 200 µl, 50 µl of medium was removed from each well for determination of IFN- γ levels, as described below. The plates were then pulsed with 1 µCi/well of tritiated thymidine for a further 18 25 hours, harvested and tritium uptake determined using a gas scintillation counter. Fractions that resulted in proliferation in both replicates three fold greater than the proliferation observed in cells cultured in medium alone were considered positive.

IFN- γ was measured using an enzyme-linked immunosorbent assay (ELISA). ELISA plates were coated with a mouse monoclonal antibody directed to 30 human IFN- γ (PharMingen, San Diego, CA) in PBS for four hours at room temperature.

- Wells were then blocked with PBS containing 5% (W/V) non-fat dried milk for 1 hour at room temperature. The plates were then washed six times in PBS/0.2% TWEEN-20 and samples diluted 1:2 in culture medium in the ELISA plates were incubated overnight at room temperature. The plates were again washed and a polyclonal rabbit
- 5 anti-human IFN- γ serum diluted 1:3000 in PBS/10% normal goat serum was added to each well. The plates were then incubated for two hours at room temperature, washed and horseradish peroxidase-coupled anti-rabbit IgG (Sigma Chemical Co., St. Louis, MO) was added at a 1:2000 dilution in PBS/5% non-fat dried milk. After a further two hour incubation at room temperature, the plates were washed and TMB substrate added.
- 10 The reaction was stopped after 20 min with 1 N sulfuric acid. Optical density was determined at 450 nm using 570 nm as a reference wavelength. Fractions that resulted in both replicates giving an OD two fold greater than the mean OD from cells cultured in medium alone, plus 3 standard deviations, were considered positive.

For sequencing, the polypeptides were individually dried onto

15 BiobreneTM (Perkin Elmer/Applied BioSystems Division, Foster City, CA) treated glass fiber filters. The filters with polypeptide were loaded onto a Perkin Elmer/Applied BioSystems Division Procise 492 protein sequencer. The polypeptides were sequenced from the amino terminal and using traditional Edman chemistry. The amino acid sequence was determined for each polypeptide by comparing the retention time of the

20 PTH amino acid derivative to the appropriate PTH derivative standards.

Using the procedure described above, antigens having the following N-terminal sequences were isolated:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Xaa-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 54)
- 25 (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 55)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 56)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 57)
- 30

- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val;
(SEQ ID No. 58)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID
No. 59)
- 5 (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Ala-Ala-Ala-
Pro-Pro-Ala; (SEQ ID No. 60) and
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-
Gly; (SEQ ID No. 61)

wherein Xaa may be any amino acid.

10 An additional antigen was isolated employing a microbore HPLC purification step in addition to the procedure described above. Specifically, 20 µl of a fraction comprising a mixture of antigens from the chromatographic purification step previously described, was purified on an Aquapore C18 column (Perkin Elmer/Applied Biosystems Division, Foster City, CA) with a 7 micron pore size, column size 1 mm x
15 100 mm, in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions were eluted from the column with a linear gradient of 1%/minute of acetonitrile (containing 0.05% TFA) in water (0.05% TFA) at a flow rate of 80 µl/minute. The eluent was monitored at 250 nm. The original fraction was separated into 4 major peaks plus other smaller components and a polypeptide was obtained which was shown to
20 have a molecular weight of 12.054 Kd (by mass spectrometry) and the following N-terminal sequence:

- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Gln-
Thr-Ser-Leu-Leu-Asn-Asn-Leu-Ala-Asp-Pro-Asp-Val-Ser-Phe-
Ala-Asp (SEQ ID No. 62).

25 This polypeptide was shown to induce proliferation and IFN-γ production in PBMC preparations using the assays described above.

Additional soluble antigens were isolated from *M. tuberculosis* culture filtrate as follows. *M. tuberculosis* culture filtrate was prepared as described above. Following dialysis against Bis-Tris propane buffer, at pH 5.5, fractionation was
30 performed using anion exchange chromatography on a Poros QE column 4.6 x 100 mm

(Perseptive Biosystems) equilibrated in Bis-Tris propane buffer pH 5.5. Polypeptides were eluted with a linear 0-1.5 M NaCl gradient in the above buffer system at a flow rate of 10 ml/min. The column eluent was monitored at a wavelength of 214 nm.

The fractions eluting from the ion exchange column were pooled and 5 subjected to reverse phase chromatography using a Poros R2 column 4.6 x 100 mm (Perseptive Biosystems). Polypeptides were eluted from the column with a linear gradient from 0-100% acetonitrile (0.1% TFA) at a flow rate of 5 ml/min. The eluent was monitored at 214 nm.

Fractions containing the eluted polypeptides were lyophilized and 10 resuspended in 80 µl of aqueous 0.1% TFA and further subjected to reverse phase chromatography on a Vydac C4 column 4.6 x 150 mm (Western Analytical, Temecula, CA) with a linear gradient of 0-100% acetonitrile (0.1% TFA) at a flow rate of 2 ml/min. Eluent was monitored at 214 nm.

The fraction with biological activity was separated into one major peak 15 plus other smaller components. Western blot of this peak onto PVDF membrane revealed three major bands of molecular weights 14 Kd, 20 Kd and 26 Kd. These polypeptides were determined to have the following N-terminal sequences, respectively:

- (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- 20 (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) and
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136), wherein Xaa may be any amino acid.

Using the assays described above, these polypeptides were shown to induce 25 proliferation and IFN- γ production in PBMC preparations. Figs. 1A and B show the results of such assays using PBMC preparations from a first and a second donor, respectively.

DNA sequences that encode the antigens designated as (a), (c), (d) and 30 (g) above were obtained by screening a genomic *M. tuberculosis* library using 32 P end labeled degenerate oligonucleotides corresponding to the N-terminal sequence and

containing *M. tuberculosis* codon bias. The screen performed using a probe corresponding to antigen (a) above identified a clone having the sequence provided in SEQ ID No. 101. The polypeptide encoded by SEQ ID No. 101 is provided in SEQ ID No. 102. The screen performed using a probe corresponding to antigen (g) above 5 identified a clone having the sequence provided in SEQ ID No. 52. The polypeptide encoded by SEQ ID No. 52 is provided in SEQ ID No. 53. The screen performed using a probe corresponding to antigen (d) above identified a clone having the sequence provided in SEQ ID No. 24, and the screen performed with a probe corresponding to antigen (c) identified a clone having the sequence provided in SEQ ID No. 25.

10 The above amino acid sequences were compared to known amino acid sequences in the gene bank using the DNA STAR system. The database searched contains some 173,000 proteins and is a combination of the Swiss, PIR databases along with translated protein sequences (Version 87). No significant homologies to the amino acid sequences for antigens (a)-(h) and (l) were detected.

15 The amino acid sequence for antigen (i) was found to be homologous to a sequence from *M. leprae*. The full length *M. leprae* sequence was amplified from genomic DNA using the sequence obtained from GENBANK. This sequence was then used to screen the *M. tuberculosis* library described below in Example 2 and a full length copy of the *M. tuberculosis* homologue was obtained (SEQ ID No. 99).

20 The amino acid sequence for antigen (j) was found to be homologous to a known *M. tuberculosis* protein translated from a DNA sequence. To the best of the inventors' knowledge, this protein has not been previously shown to possess T-cell stimulatory activity. The amino acid sequence for antigen (k) was found to be related to a sequence from *M. leprae*.

25 In the proliferation and IFN- γ assays described above, using three PPD positive donors, the results for representative antigens provided above are presented in Table 1:

TABLE 1
RESULTS OF PBMC PROLIFERATION AND IFN- γ ASSAYS

Sequence	Proliferation	IFN- γ
(a)	+	-
(c)	+++	+++
(d)	++	++
(g)	+++	+++
(h)	+++	+++

- 5 In Table 1, responses that gave a stimulation index (SI) of between 2 and 4 (compared to cells cultured in medium alone) were scored as +, an SI of 4-8 or 2-4 at a concentration of 1 μ g or less was scored as ++ and an SI of greater than 8 was scored as +++. The antigen of sequence (i) was found to have a high SI (+++) for one donor and lower SI (++) and (+) for the two other donors in both proliferation and IFN- γ assays.
- 10 These results indicate that these antigens are capable of inducing proliferation and/or interferon- γ production.

EXAMPLE 2

USE OF PATIENT SERA TO ISOLATE *M. TUBERCULOSIS* ANTIGENS

15

This example illustrates the isolation of antigens from *M. tuberculosis* lysate by screening with serum from *M. tuberculosis*-infected individuals.

Dessicated *M. tuberculosis* H37Ra (Difco Laboratories) was added to a 2% NP40 solution, and alternately homogenized and sonicated three times. The 20 resulting suspension was centrifuged at 13,000 rpm in microfuge tubes and the supernatant put through a 0.2 micron syringe filter. The filtrate was bound to Macro Prep DEAE beads (BioRad, Hercules, CA). The beads were extensively washed with 20 mM Tris pH 7.5 and bound proteins eluted with 1M NaCl. The 1M NaCl elute was dialyzed overnight against 10 mM Tris, pH 7.5. Dialyzed solution was treated with

DNase and RNase at 0.05 mg/ml for 30 min. at room temperature and then with α -D-mannosidase, 0.5 U/mg at pH 4.5 for 3-4 hours at room temperature. After returning to pH 7.5, the material was fractionated via FPLC over a Bio Scale-Q-20 column (BioRad). Fractions were combined into nine pools, concentrated in a Centriprep 10 (Amicon, Beverley, MA) and then screened by Western blot for serological activity using a serum pool from *M. tuberculosis*-infected patients which was not immunoreactive with other antigens of the present invention.

The most reactive fraction was run in SDS-PAGE and transferred to PVDF. A band at approximately 85 Kd was cut out yielding the sequence:

(m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val: (SEQ ID No. 137), wherein Xaa may be any amino acid.

Comparison of this sequence with those in the gene bank as described above, revealed no significant homologies to known sequences.

15

EXAMPLE 3

PREPARATION OF DNA SEQUENCES ENCODING *M. TUBERCULOSIS* ANTIGENS

This example illustrates the preparation of DNA sequences encoding *M. tuberculosis* antigens by screening a *M. tuberculosis* expression library with sera obtained from patients infected with *M. tuberculosis*, or with anti-sera raised against soluble *M. tuberculosis* antigens.

25 A. PREPARATION OF *M. TUBERCULOSIS* SOLUBLE ANTIGENS USING RABBIT ANTI-SERA

Genomic DNA was isolated from the *M. tuberculosis* strain H37Ra. The DNA was randomly sheared and used to construct an expression library using the Lambda ZAP expression system (Stratagene, La Jolla, CA). Rabbit anti-sera was generated against secretory proteins of the *M. tuberculosis* strains H37Ra, H37Rv and Erdman by immunizing a rabbit with concentrated supernatant of the *M. tuberculosis* cultures. Specifically, the rabbit was first immunized subcutaneously with 200 μ g of

protein antigen in a total volume of 2 ml containing 10 µg muramyl dipeptide (Calbiochem, La Jolla, CA) and 1 ml of incomplete Freund's adjuvant. Four weeks later the rabbit was boosted subcutaneously with 100 µg antigen in incomplete Freund's adjuvant. Finally, the rabbit was immunized intravenously four weeks later with 50 µg 5 protein antigen. The anti-sera were used to screen the expression library as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

10 Thirty two clones were purified. Of these, 25 represent sequences that have not been previously identified in human *M. tuberculosis*. Recombinant antigens were expressed and purified antigens used in the immunological analysis described in Example 1. Proteins were induced by IPTG and purified by gel elution, as described in Skeiky et al., *J. Exp. Med.* 181:1527-1537, 1995. Representative sequences of DNA 15 molecules identified in this screen are provided in SEQ ID Nos.: 1-25. The corresponding predicted amino acid sequences are shown in SEQ ID Nos. 63-87.

On comparison of these sequences with known sequences in the gene bank using the databases described above, it was found that the clones referred to hereinafter as TbRA2A, TbRA16, TbRA18, and TbRA29 (SEQ ID Nos. 76, 68, 70, 75) 20 show some homology to sequences previously identified in *Mycobacterium leprae* but not in *M. tuberculosis*. TbRA11, TbRA26, TbRA28 and TbDPEP (SEQ ID Nos.: 65, 73, 74, 53) have been previously identified in *M. tuberculosis*. No significant homologies were found to TbRA1, TbRA3, TbRA4, TbRA9, TbRA10, TbRA13, TbRA17, TbRa19, TbRA29, TbRA32, TbRA36 and the overlapping clones TbRA35 25 and TbRA12 (SEQ ID Nos. 63, 77, 81, 82, 64, 67, 69, 71, 75, 78, 80, 79, 66). The clone TbRa24 is overlapping with clone TbRa29.

The results of PBMC proliferation and interferon- γ assays performed on representative recombinant antigens, and using T-cell preparations from several different *M. tuberculosis*-immune patients, are presented in Tables 2 and 3, 30 respectively.

TABLE 2
RESULTS OF PBM C PROLIFERATION TO REPRESENTATIVE SOLUBLE ANTIGENS

Antigen	Patient												
	1	2	3	4	5	6	7	8	9	10	11	12	13
TbRa1	-	-	±	++	-	±	±	-	-	+	±	-	-
TbRa3	-	±	++	-	±	-	++	±	-	-	-	-	-
TbRa9	-	-	nt	nt	++	nt							
TbRa10	-	-	±	±	+	nt	±	-	+	±	±	-	-
TbRa11	±	±	+	++	+	nt	-	++	++	++	±	nt	nt
TbRa12	-	-	+	+	±	++	+	±	-	+	-	-	-
TbRa16	nt	nt	nt	nt	-	+	nt						
TbRa24	nt	nt	nt	nt	nt	-	nt						
TbRa26	-	+	nt	nt	-	nt							
TbRa29	nt	nt	nt	nt	nt	-	nt						
TbRa35	++	nt	++	++	++	nt	++	++	++	++	++	++	nt
TbRaB	nt	nt	nt	nt	-	-	nt						
TbRaC	nt	nt	nt	nt	-	-	nt						
TbRaD	nt	nt	nt	nt	-	nt							
AAMK	-	-	±	-	-	-	nt	-	-	nt	±	nt	nt
YY	-	-	-	-	-	-	nt	-	-	nt	+	nt	nt
DPEP	-	+	-	++	-	-	nt	++	±	+	±	nt	nt
Control	-	-	-	-	-	-	-	-	-	-	-	-	-

nt = not tested

TABLE 3
 RESULTS OF PBMC INTERFERON- γ PRODUCTION TO REPRESENTATIVE SOLUBLE ANTIGENS

In Tables 2 and 3, responses that gave a stimulation index (SI) of between 1.2 and 2 (compared to cells cultured in medium alone) were scored as \pm , a SI of 2-4 was scored as +, as SI of 4-8 or 2-4 at a concentration of 1 μ g or less was scored as ++ and an SI of greater than 8 was scored as +++. In addition, the effect of 5 concentration on proliferation and interferon- γ production is shown for two of the above antigens in the attached Figure. For both proliferation and interferon- γ production, TbRa3 was scored as ++ and TbRa9 as +.

These results indicate that these soluble antigens can induce proliferation and/or interferon- γ production in T-cells derived from an *M. tuberculosis*-immune 10 individual.

B. USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING M. TUBERCULOSIS ANTIGENS

The genomic DNA library described above, and an additional H37Rv 15 library, were screened using pools of sera obtained from patients with active tuberculosis. To prepare the H37Rv library, *M. tuberculosis* strain H37Rv genomic DNA was isolated, subjected to partial *Sau*3A digestion and used to construct an expression library using the Lambda Zap expression system (Stratagene, La Jolla, Ca). Three different pools of sera, each containing sera obtained from three individuals with 20 active pulmonary or pleural disease, were used in the expression screening. The pools were designated TbL, TbM and TbH, referring to relative reactivity with H37Ra lysate (*i.e.*, TbL = low reactivity, TbM = medium reactivity and TbH = high reactivity) in both ELISA and immunoblot format. A fourth pool of sera from seven patients with active pulmonary tuberculosis was also employed. All of the sera lacked increased reactivity 25 with the recombinant 38 kD *M. tuberculosis* H37Ra phosphate-binding protein.

All pools were pre-adsorbed with *E. coli* lysate and used to screen the H37Ra and H37Rv expression libraries, as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. 30 Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

Thirty two clones were purified. Of these, 31 represented sequences that had not been previously identified in human *M. tuberculosis*. Representative sequences of the DNA molecules identified are provided in SEQ ID Nos.: 26-51 and 105. Of these, TbH-8 and TbH-8-2 (SEQ. ID NO. 105) are non-contiguous DNA sequences from the same clone, and TbH-4 (SEQ. ID NO. 43) and TbH-4-FWD (SEQ. ID NO. 44) are non-contiguous sequences from the same clone. Amino acid sequences for the antigens hereinafter identified as Tb38-1, TbH-4, TbH-8, TbH-9, and TbH-12 are shown in SEQ ID Nos.: 88-92. Comparison of these sequences with known sequences in the gene bank using the databases identified above revealed no significant homologies to TbH-4, TbH-8, TbH-9 and TbM-3, although weak homologies were found to TbH-9. TbH-12 was found to be homologous to a 34 kD antigenic protein previously identified in *M. paratuberculosis* (Acc. No. S28515). Tb38-1 was found to be located 34 base pairs upstream of the open reading frame for the antigen ESAT-6 previously identified in *M. bovis* (Acc. No. U34848) and in *M. tuberculosis* (Sorensen et al., *Infec. Immun.* 63:1710-1717, 1995).

Probes derived from Tb38-1 and TbH-9, both isolated from an H37Ra library, were used to identify clones in an H37Rv library. Tb38-1 hybridized to Tb38-1F2, Tb38-1F3, Tb38-1F5 and Tb38-1F6 (SEQ. ID NOS. 112, 113, 116, 118, and 119). (SEQ ID NOS. 112 and 113 are non-contiguous sequences from clone Tb38-1F2.) Two open reading frames were deduced in Tb38-1F2; one corresponds to Tb37FL (SEQ. ID. NO. 114), the second, a partial sequence, may be the homologue of Tb38-1 and is called Tb38-IN (SEQ. ID NO. 115). The deduced amino acid sequence of Tb38-1F3 is presented in SEQ. ID. NO. 117. A TbH-9 probe identified three clones in the H37Rv library: TbH-9-FL (SEQ. ID NO. 106), which may be the homologue of TbH-9 (R37Ra), TbH-9-1 (SEQ. ID NO. 108), and TbH-9-4 (SEQ. ID NO. 110), all of which are highly related sequences to TbH-9. The deduced amino acid sequences for these three clones are presented in SEQ ID NOS. 107, 109 and 111.

The results of T-cell assays performed on Tb38-1, ESAT-6 and other representative recombinant antigens are presented in Tables 4A, B and 5, respectively, below:

TABLE 4A
RESULTS OF PBMC PROLIFERATION TO REPRESENTATIVE ANTIGENS

Antigen	Donor										
	1	2	3	4	5	6	7	8	9	10	11
Tb38.1	+++	+	-	-	-	++	-	+	-	++	+++
ESAT-6	+++	+	+	+	-	+	-	+	+	++	+++
TbH-9	++	++	-	++	±	±	++	++	++	++	++

5

TABLE 4B
RESULTS OF PBMC INTERFERON-γ PRODUCTION TO REPRESENTATIVE ANTIGENS

Antigen	Donor										
	1	2	3	4	5	6	7	8	9	10	11
Tb38.1	+++	+	-	+	+	+++	-	++	-	+++	+++
ESAT-6	+++	+	+	+	+-	+	-	+	+	+++	+++
TbH-9	++	++	-	+++	±	±	+++	+++	++	+++	++

10

TABLE 5
SUMMARY OF T-CELL RESPONSES TO REPRESENTATIVE ANTIGENS

Antigen	Proliferation			Interferon- γ			total
	patient 4	patient 5	patient 6	patient 4	patient 5	patient 6	
TbH9	++	++	++	+++	++	++	13
TbM7	-	+	-	++	+	-	4
TbH5	-	+	+	++	++	++	8
TbL23	-	+	\pm	++	++	+	7.5
TbH4	-	++	\pm	++	++	\pm	7
- control	-	-	-	-	-	-	0

5

These results indicate that both the inventive *M. tuberculosis* antigens and ESAT-6 can induce proliferation and/or interferon- γ production in T-cells derived from an *M. tuberculosis*-immune individual. To the best of the inventors' knowledge, ESAT-6 has not been previously shown to stimulate human immune responses

- 10 A set of six overlapping peptides covering the amino acid sequence of the antigen Tb38-1 was constructed using the method described in Example 4. The sequences of these peptides, hereinafter referred to as pep1-6, are provided in SEQ ID Nos. 93-98, respectively. The results of T-cell assays using these peptides are shown in Tables 6 and 7. These results confirm the existence, and help to localize T-cell epitopes
- 15 within Tb38-1 capable of inducing proliferation and interferon- γ production in T-cells derived from an *M. tuberculosis* immune individual.

TABLE 6
RESULTS OF PBMC PROLIFERATION TO TB38-1 PEPTIDES

TABLE 7
RESULTS OF PBMC INTERFERON- γ PRODUCTION TO Tb38-1 PEPTIDES

EXAMPLE 4PURIFICATION AND CHARACTERIZATION OF A POLYPEPTIDE FROM TUBERCULIN PURIFIED PROTEIN DERIVATIVE

5

An *M. tuberculosis* polypeptide was isolated from tuberculin purified protein derivative (PPD) as follows.

PPD was prepared as published with some modification (Seibert, F. et al., Tuberculin purified protein derivative. Preparation and analyses of a large quantity 10 for standard. The American Review of Tuberculosis 44:9-25, 1941).

M. tuberculosis Rv strain was grown for 6 weeks in synthetic medium in roller bottles at 37°C. Bottles containing the bacterial growth were then heated to 100° C in water vapor for 3 hours. Cultures were sterile filtered using a 0.22 µ filter and the liquid phase was concentrated 20 times using a 3 kD cut-off membrane. Proteins were 15 precipitated once with 50% ammonium sulfate solution and eight times with 25% ammonium sulfate solution. The resulting proteins (PPD) were fractionated by reverse phase liquid chromatography (RP-HPLC) using a C18 column (7.8 x 300 mM; Waters, Milford, MA) in a Biocad HPLC system (Perseptive Biosystems, Framingham, MA). Fractions were eluted from the column with a linear gradient from 0-100% buffer (0.1% 20 TFA in acetonitrile). The flow rate was 10 ml/minute and eluent was monitored at 214 nm and 280 nm.

Six fractions were collected, dried, suspended in PBS and tested individually in *M. tuberculosis*-infected guinea pigs for induction of delayed type hypersensitivity (DTH) reaction. One fraction was found to induce a strong DTH 25 reaction and was subsequently fractionated further by RP-HPLC on a microbore Vydac C18 column (Cat. No. 218TP5115) in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions were eluted with a linear gradient from 5-100% buffer (0.05% TFA in acetonitrile) with a flow rate of 80 µl/minute. Eluent was monitored at 215 nm. Eight fractions were collected and tested for induction of DTH in *M. 30 tuberculosis*-infected guinea pigs. One fraction was found to induce strong DTH of

about 16 mm induration. The other fractions did not induce detectable DTH. The positive fraction was submitted to SDS-PAGE gel electrophoresis and found to contain a single protein band of approximately 12 kD molecular weight.

This polypeptide, herein after referred to as DPPD, was sequenced from 5 the amino terminal using a Perkin Elmer/Applied Biosystems Division Procise 492 protein sequencer as described above and found to have the N-terminal sequence shown in SEQ ID No.: 129. Comparison of this sequence with known sequences in the gene bank as described above revealed no known homologies. Four cyanogen bromide fragments of DPPD were isolated and found to have the sequences shown in SEQ ID 10 Nos.: 130-133.

The ability of the antigen DPPD to stimulate human PBMC to proliferate and to produce IFN- γ was assayed as described in Example 1. As shown in Table 8, DPPD was found to stimulate proliferation and elicit production of large quantities of IFN- γ ; more than that elicited by commercial PPD.

15

TABLE 8
RESULTS OF PROLIFERATION AND INTERFERON- γ ASSAYS TO DPPD

PBMC Donor	Stimulator	Proliferation (CPM)	IFN- γ (OD ₄₅₀)
A	Medium	1,089	0.17
	PPD (commercial)	8,394	1.29
	DPPD	13,451	2.21
B	Medium	450	0.09
	PPD (commercial)	3,929	1.26
	DPPD	6,184	1.49
C	Medium	541	0.11
	PPD (commercial)	8,907	0.76
	DPPD	23,024	>2.70

EXAMPLE 5SYNTHESIS OF SYNTHETIC POLYPEPTIDES

5

- Polypeptides may be synthesized on a Millipore 9050 peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray mass spectrometry and by amino acid analysis.
- From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANTS: Corixa Corporation
- (ii) TITLE OF INVENTION: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND DIAGNOSIS OF TUBERCULOSIS
- (iii) NUMBER OF SEQUENCES: 137
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: SEED and BERRY LLP
 - (B) STREET: 6300 Columbia Center, 701 Fifth Avenue
 - (C) CITY: Seattle
 - (D) STATE: Washington
 - (E) COUNTRY: USA
 - (F) ZIP: 98104-7092
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0. Version #1.30
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE: 27-AUG-1996
 - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Maki, David J.
 - (B) REGISTRATION NUMBER: 31,392
 - (C) REFERENCE/DOCKET NUMBER: 210121.411PC
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: (206) 622-4900
 - (B) TELEFAX: (206) 682-6031

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 766 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGAGGCACCG	GTAGTTGAA	CCAAACGCAC	AATCGACGGG	CAAACGAACG	GAAGAACACA	60
ACCATGAAGA	TGGTGAAATC	GATCGCCGCA	GGTCTGACCG	CCGCGGCTGC	AATCGGCGCC	120
GCTGCGGCCG	GTGTGACTTC	GATCATGGCT	GGCGGCCCGG	TCGTATACCA	GATGCAGCCG	180
GTCGTCTTCG	GCGCGCCACT	GCCGTTGGAC	CCGGCATCCG	CCCCTGACGT	CCCGACCGCC	240
GCCCAGTTGA	CCAGCCTGCT	CAACAGCCTC	GCCGATCCCA	ACGTGTCGTT	TGCGAACAAAG	300
GGCAGTCTGG	TCGAGGGCGG	CATCGGGGGC	ACCGAGGCGC	GCATCGCCGA	CCACAAGCTG	360
AAGAAGGCCG	CCGAGCACCG	GGATCTGCCG	CTGTCGTTCA	GCGTGACGAA	CATCCAGCCG	420
GCGGCCGCCG	GTTCGGCCAC	CGCCGACGTT	TCCGTCTCGG	GTCCGAAGCT	CTCGTCGCCG	480
GTCACGCAGA	ACGTACGTT	CGTGAATCAA	GGCGGCTGGA	TGCTGTCACG	CGCATCGGCG	540
ATGGAGTTGC	TGCAGGCCGC	AGGGNAACTG	ATTGGCGGGC	CGGNNTTCAGC	CCGCTGTTCA	600
GCTACGCCGC	CCGCCTGGTG	ACGCGTCCAT	GTCGAACACT	CGCGCGTGT	GCACGGTGCG	660
GTNTGCGCAG	GGNCGCACGC	ACCGCCCGGT	GCAAGCCGTC	CTCGAGATAG	GTGGTGNCTC	720
GNCACCAGNG	ANCACCCCCN	NNTCGNCNN	TCTCGNTGNT	GNATGA		766

(2) INFORMATION FOR SEQ ID NO:2:

- (A) LENGTH: 752 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATGCATCACC ATCACCATCA CGATGAAGTC ACGGTAGAGA CGACCTCCGT CTTCCGCGCA	60
GACTTCCTCA GCGAGCTGGA CGCTCCTGCG CAAGCGGGTA CGGAGAGCGC GGTCTCCGGG	120
GTGGAAGGGC TCCCGCCGGG CTCGGCGTTG CTGGTAGTCA AACGAGGCC CAACGCCGGG	180
TCCCGGTTCC TACTCGACCA AGCCATCACG TCGGCTGGTC GGCATCCCAGA CAGCGACATA	240
TTTCTCGACG ACGTGACCGT GAGCCGTCGC CATGCTGAAT TCCGGTTGGA AAACAACGAA	300
TTCAATGTCG TCGATGTCGG GAGTCTCAAC GGCACCTACG TCAACCGCGA GCCCGTGGAT	360
TCGGCGGTGC TGGCGAACGG CGACGAGGTC CAGATCGGCA AGCTCCGGTT GGTGTTCTTG	420
ACCGGACCCA AGCAAGGCGA GGATGACGGG AGTACCGGGG GCCCGTGAGC GCACCCGATA	480
GCCCCGCGCT GGCCGGGATG TCGATCGGGG CGGTCCCTCCG ACCTGCTACG ACCGGATTTT	540
CCCTGATGTC CACCATCTCC AAGATTGAT TCTTGGGAGG CTTGAGGGTC NGGGTGACCC	600
CCCCGCGGGC CTCATTCNGG GGTNTCGGCN GGTTTCACCC CNTACCNACT GCCNCCCGGN	660
TTGCNAATTG NTTCTTCNCT GCCCNAAAG GGACCNNTAN CTTGCCGCTN GAAANGGTNA	720
TCCNGGGCCC NTCCTNGAAN CCCCNCCCC CT	752

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 813 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATATGCATC ACCATCACCA TCACACTTCT AACCGCCCAG CGCGTCGGGG GCGTCGAGCA	60
CCACGCGACA CCGGGCCCGA TCGATCTGCT AGCTTGAGTC TGGTCAGGCA TCGTCGTCAG	120
CAGCGCGATG CCCTATGTTT GTCGTGACT CAGATATCGC GGCAATCCAA TCTCCCGCCT	180
GCGGCCGGCG GTGCTGCAA CTACTCCGG AGGAATTTCG ACGTGCGCAT CAAGATCTTC	240
ATGCTGGTCA CGGCTGTCGT TTTGCTCTGT TGTTCGGGTG TGGCCACGGC CGCGCCCAAG	300
ACCTACTGCG AGGAGTTGAA AGGCACCGAT ACCGGCCAGG CGTGCCAGAT TCAAATGTCC	360
GACCCGGCCT ACAACATCAA CATCAGCCTG CCCAGTTACT ACCCCGACCA GAAGTCGCTG	420
GAAAATTACA TCGCCCAGAC GCGCGACAAG TTCCTCAGCG CGGCCACATC GTCCACTCCA	480
CGCGAACGCC CCTACGAATT GAATATCACC TCGGCCACAT ACCAGTCGC GATAACGCCG	540
CGTGGTACGC AGGCCGTGGT GCTCAMGGTC TACCACAACG CCGGCGGCAC GCACCCAACG	600
ACCACGTACA AGGCCTTCGA TTGGGACCAAG GCCTATCGCA AGCCAATCAC CTATGACACG	660
CTGTGGCAGG CTGACACCGA TCCGCTGCCA GTCGTCTTCC CCATTGTTGC AAGGTGAACT	720
GAGCAACGCA GACCGGGACA ACWGGTATCG ATAGCCGCCN AATGCCGGCT TGGAACCCNG	780
TGAAATTATC ACAACTTCGC AGTCACNAAA NAA	813

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 447 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CGGTATGAAC ACGGCCGCGT CCGATAACTT CCAGCTGTCC CAGGGTGGGC AGGGATT CGC	60
CATTCCGATC GGGCAGGCGA TGGCGATCGC GGGCCAGATC CGATCGGGTG GGGGGTCACC	120
CACCGTTCAT ATCGGGCCTA CCGCCTTCCT CGGCTTGGGT GTTGTGACA ACAACGGCAA	180
CGGCGCACGA GTCCAACGCG TGTCGGGAG CGCTCCGGCG GCAAGTCTCG GCATCTCCAC	240
CGGCGACGTG ATCACCGCGG TCGACGGCGC TCCGATCAAC TCAGGCCACCG CGATGGCGGA	300
CGCGCTTAAC GGGCATCATC CCGGTGACGT CATCTCGGTG AACTGGCAA CCAAGTCGGG	360
CGGCACGCGT ACAGGGAACG TGACATTGGC CGAGGGACCC CCGGCCTGAT TTCTGTCGYGG	420
ATACCACCCG CGGGCCGGCC AATTGGA	447

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 604 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GTCCCAC TGC GGTCGCCGAG TATGTCGCC AGCAAATGTC TGGCAGCCGC CCAACGGAAT	60
CCGGTGATCC GACGTCGCAG GTTGTGAAAC CCGCCGCCGC GGAAGTATCG GTCCATGCCT	120
AGCCC GGCGA CGGCGAGCGC CGGAATGGCG CGAGTGAGGA GGC GGGCAAT TTGGCGGGGC	180
CCGGCGACGG NGAGCGCCGG AATGGCGCGA GTGAGGGAGGT GGNCAGTCAT GCCCAGNGTG	240
ATCCAATCAA CCTGNATTG GNCTGNGGGN CCATTTGACA ATCGAGGTAG TGAGCGCAA	300
TGAATGATGG AAAACGGGNG GNGACGTCCG NTGTTCTGGT GGTGNTAGGT GNCTGNCTGG	360

NGTNGNGGNT ATCAGGATGT TCTTCGNCGA AANCTGATGN CGAGGAACAG GGTGTNCCCG	420
NNANNCCNAN GGNGTCCNAN CCCNNNNTCC TCGNCGANAT CANANAGNCG NTTGATGNGA	480
NAAAAGGGTG GANCAGNNNN AANTNGNGGN CCNAANAANC NNNANNGNNG NNAGNTNGNT	540
NNNTNTNNNC ANNNNNNNNTG NNGNNGNNCN NNCAANCNN NTNNNNNGNAA NNGGNTTNTT	600
NAAT	604

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 633 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TTGCANGTCG AACCACCTCA CTAAAGGGAA CAAAAGCTNG AGCTCCACCG CGGTGGCGGC	60
CGCTCTAGAA CTAGTGKATM YYYCKGGCTG CAGSAATYCG GYACGAGCAT TAGGACAGTC	120
TAACGGTCCT GTTACGGTGA TCGAATGACC GACGACATCC TGCTGATCGA CACCGACGAA	180
CGGGTGCAGAA CCCTCACCCCT CAACCGGCCG CAGTCCCAYA ACGCGCTCTC GGCGGCGCTA	240
CGGGATCGGT TTTTCGCGGY GTTGGYCGAC GCCGAGGYCG ACGACGACAT CGACGTCGTC	300
ATCCTCACCG GYGCCGATCC GGTGTTCTGC GCCGGACTGG ACCTCAAGGT AGCTGGCCGG	360
GCAGACCGCG CTGCCGGACA TCTCACCGCG GTGGGCGGCC ATGACCAAGC CGGTGATCGG	420
CGCGATCAAAC GGCGCCGCGG TCACCGGCAG GCTCGAACTG GCGCTGTACT GCGACATCCT	480
GATCGCCTCC GAGCACGCC GCTTCGNCGA CACCCACGCC CGGGTGGGGC TGCTGCCAC	540
CTGGGGACTC AGTGTGTGCT TGCCGCAAAA GGTGGCATC GGNCTGGGCC GGTGGATGAG	600
CCTGACCGGC GACTACCTGT CCGTGACCGA CGC	633

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1362 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CGACGACGAC GGCGCCGGAG AGCGGGCGCG AACGGCGATC GACGCGGCC	TGGCCAGAGT	60
CGGCACCACC CAGGAGGGAG TCGAACATG AAATTTGTCA ACCATATTGA	GCCCCTCGCG	120
CCCCGCCGAG CCGGCGGCCGC GGTCGCCGAG GTCTATGCCG AGGCCCGCCG	CGAGTTCGGC	180
CGGCTGCCCG AGCCGCTCGC CATGCTGTCC CCGGACGAGG GACTGCTCAC	CGCCGGCTGG	240
GCGACGTTGC GCGAGACACT GCTGGTGGC CAGGTGCCGC GTGGCCGCAA	GGAAGCCGTC	300
GCCGCCGCCG TCGCGGCCAG CCTGCGCTGC CCCTGGTGC	TCGACGCACA CACCACCATG	360
CTGTACGCGG CAGGCCAAC CGACACCGCC GCGCGATCT TGGCCGGCAC	AGCACCTGCC	420
GCCGGTGACC CGAACGCGCC GTATGTGGCG TGGCGGGCAG GAACCGGGAC	ACCGGGGGGA	480
CCGCCGGCAC CGTCGGCCC GGATGTCGCC GCCGAATACC TGGGCACCGC	GGTGCAATTG	540
CACTTCATCG CACGCCCTGGT CCTGGTGCTG CTGGACGAAA CCTTCCTGCC	GGGGGGCCCG	600
CGCGCCCAAC AGCTCATGCG CCGCGCCGGT GGACTGGTGT TCGCCCGCAA	GGTGCACGCG	660
GAGCATCGGC CGGGCCGCTC CACCCGCCGG CTCGAGCCGC GAACGCTGCC	CGACGATCTG	720
GCATGGCAA CACCGTCCGA GCCCATAGCA ACCCGCGTTCG CCGCGCTCAG	CCACCACTG	780
GACACCGCGC CGCACCTGCC GCCACCGACT CGTCAGGTGG TCAGGGCGGGT	CGTGGGGTCG	840
TGGCACGGCG AGCCAATGCC GATGAGCAGT CGCTGGACGA ACGAGCACAC	CGCCGAGCTG	900

CCCGCCGACC TGCACGCGCC CACCCGTCTT GCCCTGCTGA CGGGCCTGGC CCCGCATCAG	960
GTGACCGACG ACGACGTCGC CGCGGCCCGA TCCCTGCTCG ACACCGATGC GGCGCTGGTT	1020
GGCGCCCTGG CCTGGGCCGC CTTCACCGCC GCGCGGCCGA TCAGCACCTG GATCGGCGCC	1080
GCCGCCGAGG GCCAGGTGTC GCGGCAAAAC CCGACTGGGT GAGTGTGCGC GCCCTGTCGG	1140
TAGGGTGTCA TCGCTGGCCC GAGGGATCTC GCGGCGGCCGA ACGGAGGTGG CGACACAGGT	1200
GGAAGCTGCG CCCACTGGCT TGCGCCCCAA CGCCGTCGTG GGCGTTCGGT TGCCCGCACT	1260
GGCCGATCAG GTCGGCGCCG GCCCTGGCC GAAGGTCCAG CTCAACGTGC CGTCACCGAA	1320
GGACCGGACG GTCACCGGGG GTCACCCCTGC GCGCCAAGG AA	1362

(2) INFORMATION FOR SEQ ID NO:8:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1458 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GCGACGACCC CGATATGCCG GGCACCGTAG CGAAAGCCGT CGCCGACGCA CTCGGGCGCG	60
GTATCGCTCC CGTTGAGGAC ATTCAAGGACT GCGTGGAGGC CGGGCTGGGG GAAGCCGGTC	120
TGGATGACGT GGCCCGTGT TACATCATCT ACCGGCAGCG GCGCGCCGAG CTGCGGACGG	180
CTAAGGCCTT GCTCGCGTG CGGGACGAGT TAAAGCTGAG CTTGGCGGCC GTGACGGTAC	240
TGCGCGAGCG CTATCTGCTG CACGACGAGC AGGGCCGGCC GGCGAGTCG ACCGGCGAGC	300
TGATGGACCG ATCGGCGCGC TGTGTCGCGG CGGCCGAGGA CCAGTATGAG CCGGGCTCGT	360
CGAGGGCGGTG GGCGAGCGG TTGCCCCACGC TATTACGCAA CCTGGAATTG CTGCCGAATT	420
CGCCCACGTT GATGAACCTCT GGCACCGACC TGGGACTGCT CGCCGGCTGT TTTGTTCTGC	480

CGATTGAGGA TTGCGCTGCAA TCGATCTTTC CGACGCTGGG ACAGGCCGCC GAGCTGCAGC	540
GGGCTGGAGG CGGCACCGGA TATGCGTTCA GCCACCTGCG ACCCGCCGGG GATCGGGTGG	600
CCTCCACGGG CGGCACGGCC AGCGGACCGG TGTCGTTCT ACGGCTGTAT GACAGTGCCG	660
CGGGTGTGGT CTCCATGGGC GGTCGCCGGC GTGGCGCCTG TATGGCTGTG CTTGATGTGT	720
CGCACCCGGA TATCTGTGAT TTGCGTACCG CCAAGGCCGA ATCCCCCAGC GAGCTCCCGC	780
ATTTCAACCT ATCGGTTGGT GTGACCGACG CGTTCTGCG GGCCGTCGAA CGCAACGGCC	840
TACACCGGCT GGTCAATCCG CGAACCGGCA AGATCGTCGC GCGGATGCCCG GCCGCCGAGC	900
TGTTCGACGC CATCTGCAA GCCGCGCACG CCGGTGGCGA TCCCAGGCTG GTGTTCTCG	960
ACACGATCAA TAGGGCAAAAC CCGGTGCCGG GGAGAGGCCG CATCGAGGCG ACCAACCCGT	1020
GCGGGGAGGT CCCACTGCTG CCTTACGAGT CATGTAATCT CGGCTCGATC AACCTCGCCC	1080
GGATGCTCGC CGACGGTCGC GTGACTGGG ACCGGCTCGA GGAGGTCGCC GGTGTGGCGG	1140
TGCGGTTCCCT TGATGACGTC ATCGATGTCA GCCGCTACCC CTTCCCCGAA CTGGGTGAGG	1200
CGGCCCGCGC CACCCGCAAG ATCGGGCTGG GAGTCATGGG TTTGGCGGAA CTGCTTGCCG	1260
CACTGGGTAT TCCGTACGAC AGTGAAGAAG CCGTGCGGTT AGCCACCCGG CTCATGCGTC	1320
GCATACAGCA GGCGCGCAC ACGGCATCGC GGAGGCTGGC CGAAGAGCGG GGCGCATTCC	1380
CGCGTTCAC CGATAGCCGG TTCGCGCGGT CGGGCCCGAG GCGCAACGCA CAGGTCACCT	1440
CCGTCGCTCC GACGGGCA	1458

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 862 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ACGGTGTAAAT	CGTGCTGGAT	CTGGAACCGC	GTGGCCCGCT	ACCTACCGAG	ATCTACTGGC	60
GGCGCAGGGG	GCTGGCCCTG	GGCATCGCGG	TCGTCGTAGT	CGGGATCGCG	GTGCCATCG	120
TCATCGCCTT	CGTCGACAGC	AGCGCCGGTG	CCAAACCGGT	CAGCGCCGAC	AAGCCGGCCT	180
CCGCCCAGAG	CCATCCGGGC	TCGCCGGCAC	CCCAAGCACC	CCAGCCGGCC	GGGCAAACCG	240
AAGGTAACGC	CGCCGCGGCC	CCGCCGCAGG	GCCAAAACCC	CGAGACACCC	ACGCCCACCG	300
CCGCGGTGCA	GCCGCCGCG	GTGCTCAAGG	AAGGGGACGA	TTGCCCCGAT	TCGACGCTGG	360
CCGTCAAAGG	TTTGACCAAC	GCGCCGCAGT	ACTACGTCGG	CGACCAGCCG	AAGTTCACCA	420
TGGTGGTCAC	CAACATCGGC	CTGGTGTCT	GTAAACGCGA	CGTTGGGCC	GCGGTGTTGG	480
CCGCCTACGT	TTACTCGCTG	GACAACAAGC	GGTTGTGGTC	CAACCTGGAC	TGCGCGCCCT	540
CGAATGAGAC	GCTGGTCAAG	ACGTTTCCC	CCGGTGAGCA	GGTAACGACC	GCGGTGACCT	600
GGACCGGGAT	GGGATCGGCG	CCGCGCTGCC	CATTGCCGCG	GCCGGCGATC	GGGCCGGGCA	660
CCTACAATCT	CGTGGTACAA	CTGGGCAATC	TGCCGCTCGCT	GCCGGTTCCG	TTCATCCTGA	720
ATCAGCCGCC	GCCGCCGCC	GGGCCGGTAC	CCGCTCCGGG	TCCAGCGCAG	GCGCCTCCGC	780
CGGAGTCTCC	CGCGCAAGGC	GGATAATTAT	TGATCGCTGA	TGGTCGATTC	CGCCAGCTGT	840
GACAACCCCT	CGCCTCGTGC	CG				862

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 622 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAAGGTGAC CAATGACAAA	60
GACACCCCGG GCGCCAAGAT CGTCGAAGTA GTGGCCGGTG GTGCTGCCGC GAACGCTGGA	120
GTGCCGAAGG GCGTCGTTGT CACCAAGGTC GACGACCGCC CGATCAACAG CGCGGACGCG	180
TTGGTTGCCG CCGTGCCTGTC CAAAGCGCCG GGCGCCACGG TGGCGCTAAC CTTTCAGGAT	240
CCCTCGGGCG GTAGCCGCAC AGTGCAAGTC ACCCTCGGCA AGGCAGGAGCA GTGATGAAGG	300
TCGCCGCGCA GTGTTCAAAG CTCGGATATA CGGTGGCACCC CATGGAACAG CGTGCAGGAGT	360
TGGTGGTTGG CGGGCACTT GTCGTCGTCG TTGACGATCG CACGGCGCAC GGCGATGAAG	420
ACCACAGCGG GCCGCTTGTC ACCGAGCTGC TCACCGAGGC CGGGTTGTT GTCGACGGCG	480
TGGTGGCGGT GTCGGCCGAC GAGGTCGAGA TCCGAAATGC GCTGAACACA GCGGTGATCG	540
GCGGGGTGGA CCTGGTGGTG TCGGTCGGCG GGACCGGNGT GACGNCTCGC GATGTCACCC	600
CGGAAGCCAC CCGNGACATT CT	622

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1200 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGCGCAGCGG TAAGCCTGTT GGCCGCCGGC ACACCTGGTGT TGACAGCATG CGGCGGTGGC	60
ACCAACAGCT CGTCGTCAGG CGCAGGCGGA ACGTCTGGGT CGGTGCACTG CGGCGGCAAG	120
AAGGAGCTCC ACTCCAGCGG CTCGACCGCA CAAGAAAATG CCATGGAGCA GTTCGTCTAT	180

GCCTACGTGC GATCGTGCCC	240
GGGCTACACG TTGGACTACA ACGCCAACGG	
GTCCGGTGCC	
GGGGTGACCC AGTTTCTCAA CAACGAAACC	300
GATTTCGCCG GCTCGGATGT CCCGTTGAAT	
CCGTCGACCG GTCAACCTGA CCGGTCGGCG	360
GAGCGGTGCG GTTCCCCGC ATGGGACCTG	
CCGACGGTGT TCGGCCCGAT CGCGATCACC	420
TACAATATCA AGGGCGTGAG CACGCTGAAT	
CTTGACGGAC CCACTACCGC	480
CAAGATTTTC AACGGCACCA TCACCGTGTG	
GAATGATCCA	
CAGATCCAAG CCCTCAACTC CGGCACCGAC	540
CTGCCGCCAA CACCGATTAG CGTTATCTTC	
CGCAGCGACA AGTCCGGTAC	600
GTGGACAAC TTCCAGAAAT ACCTCGACGG	
TGTATCCAAC	
GGGGCGTGGG GCAAAGGCGC	660
CAGCGAAACG TTCAGCGGGG	
GCGTCGGCGT CGGCGCCAGC	
GGGAACAAACG AACGTCGGC	720
CCTACTGCAG ACGACCGACG	
GGTCGATCAC CTACAACGAG	
TGGTCGTTTG CGGTGGTAA	780
GCAGTTAAC	
ATGGCCCAGA TCATCACGTC	
GGCGGGTCCG	
GATCCAGTGG CGATCACAC	840
CGAGTCGGTC GGTAAGACAA	
TCGCCGGGC CAAGATCATG	
GGACAAGGCA ACGACCTGGT	900
ATTGGACACG TCGTCGTTCT	
ACAGACCCAC CCAGCCTGGC	
TCTTACCCGA TCGTGCTGGC	960
GACCTATGAG ATCGTCTGCT	
CGAAATACCC GGATGCGACG	
ACCGGTACTG CGGTAAAGGGC	1020
GTTTATGCAA GCCGCGATTG	
GTCCAGGCCA AGAAGGCCTG	
GACCAATACG GCTCCATTCC	1080
GTTGCCAAA TCGTTCCAAG	
CAAAATTGGC GGCGCGGGTG	
AATGCTATTT CTTGACCTAG	1140
TGAAGGGAAT TCGACGGTGA	
GCGATGCCGT TCCGCAGGTA	
GGGTCGCAAT TTGGGCCGTA	1200
TCAGCTATTG CGGCTGCTGG	
GCCGAGGCAG	
GATGGGCGAG	

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1155 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GCAAGCAGCT	GCAGGTCGTG	CTGTCGACG	AACTGGGCAT	GCCGAAGACC	AAACGCACCA	60
AGACCGGCTA	CACCACGGAT	GCCGACGCGC	TGCAGTCGTT	GTTCGACAAG	ACCGGGCATC	120
CGTTTCTGCA	ACATCTGCTC	GCCCACCGCG	ACGTCACCCG	GCTCAAGGTC	ACCGTCGACG	180
GGTTGCTCCA	AGCGGTGGCC	GCCGACGGCC	GCATCCACAC	CACGTTAAC	CAGACGATCG	240
CCGCGACCGG	CCGGCTCTCC	TCGACCGAAC	CCAACCTGCA	GAACATCCCG	ATCCGCACCG	300
ACGCGGGCCG	GCGGATCCGG	GACGCGTTCG	TGGTCGGGGA	CGGTTACGCC	GAGTTGATGA	360
CGGCCGACTA	CAGCCAGATC	GAGATGCGGA	TCATGGGGCA	CCTGTCCGGG	GACGAGGGCC	420
TCATCGAGGC	GTTAACACCC	GGGGAGGACC	TGTATTGTT	CGTCGCGTCC	CGGGTGTTCG	480
GTGTGCCCAT	CGACGAGGTC	ACCGGCGAGT	TGCGGCGCCG	GGTCAAGGCG	ATGTCCTACG	540
GGCTGGTTTA	CGGGTTGAGC	GCCTACGGCC	TGTCGCAGCA	GTTGAAAATC	TCCACCGAGG	600
AAGCCAACGA	GCAGATGGAC	GCGTATTCG	CCCGATTGG	CGGGGTGCGC	GACTACCTGC	660
GCGCCGTAGT	CGAGCGGGCC	CGCAAGGACG	GCTACACCTC	GACGGTGCTG	GGCCGTCGCC	720
GCTACCTGCC	CGAGCTGGAC	AGCAGCAACC	GTCAAGTGC	GGAGGCCGCC	GAGCGGGCGG	780
CGCTGAACGC	GCCGATCCAG	GGCAGCGCG	CCGACATCAT	CAAGGTGGCC	ATGATCCAGG	840
TCGACAAGGC	GCTCAACGAG	GCACAGCTGG	CGTCGCGCAT	GCTGCTGCAG	GTCCACGACG	900
AGCTGCTGTT	CGAAATCGCC	CCCGGTGAAC	GCGAGCGGGT	CGAGGCCCTG	GTGCGCGACA	960
AGATGGCGG	CGCTTACCCG	CTCGACGTCC	CGCTGGAGGT	GTCGGTGGC	TACGGCCGCA	1020
GCTGGGACGC	GGCGGCGCAC	TGAGTGCCGA	GCGTGCATCT	GGGGCGGGAA	TTCGGCGATT	1080
TTTCCGCCCT	GAGTTCACGC	TCGGCGCAAT	CGGGACCGAG	TTTGTCCAGC	GTGTACCCGT	1140
CGAGTAGCCT	CGTCA					1155

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1771 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAGCGCCGTC	TGGTGTGTTGA	ACGGTTTAC	CGGTCGGCAT	CGGCACGGGC	GTTGCCGGGT	60
TCGGGCCTCG	GGTTGGCGAT	CGTCAAACAG	GTGGTGCTCA	ACCACGGCGG	ATTGCTGCGC	120
ATCGAAGACA	CCGACCCAGG	CGGCCAGCCC	CCTGGAACGT	CGATTTACGT	GCTGCTCCCC	180
GGCCGTGCGA	TGCCGATTCC	GCAGCTTCCC	GGTGCACGG	CTGGCGCTCG	GAGCACGGAC	240
ATCGAGAACT	CTCGGGGTTTC	GGCGAACGTT	ATCTCAGTGG	AATCTCAGTC	CACGCGCGCA	300
ACCTAGTTGT	GCAGTTACTG	TTGAAAGCCA	CACCCATGCC	AGTCCACGCA	TGGCCAAGTT	360
GGCCCGAGTA	GTGGGCCTAG	TACAGGAAGA	GCAACCTAGC	GACATGACGA	ATCACCCACG	420
GTATTGCCA	CCGCCGCAGC	AGCCGGGAAC	CCCAGGTTAT	GCTCAGGGGC	AGCAGCAAAC	480
GTACAGCCAG	CAGTTGACT	GGCGTTACCC	ACCGTCCCCG	CCCCCGCAGC	CAACCCAGTA	540
CCGTCAACCC	TACGAGGCGT	TGGGTGGTAC	CCGGCCGGGT	CTGATACTG	GCGTGATTCC	600
GACCATGACG	CCCCCTCCTG	GGATGGTTCG	CCAACGCCCT	CGTGCAGGCA	TGTTGCCAT	660
CGGCGCGGTG	ACGATAGCGG	TGGTGTCCGC	CGGCATCGGC	GGCGCGGCCG	CATCCCTGGT	720
CGGGTTCAAC	CGGGCACCCG	CGGGCCCCAG	CGGCAGGCCA	GTGGCTGCCA	GCGCGCGGCC	780
AAGCATCCCC	GCAGCAAACA	TGCCGCCGGG	GTCGGTCGAA	CAGGTGGCGG	CCAAGGTGGT	840
GCCCAGTGTC	GTCATGTTGG	AAACCGATCT	GGGCCGCCAG	TCGGAGGAGG	GCTCCGGCAT	900
CATTCTGTCT	GCCGAGGGGC	TGATCTTGAC	CAACAACCAC	GTGATCGCGG	CGGCCGCCAA	960

GCCTCCCTG GGCAGTCCGC CGCCGAAAAC GACGGTAACC TTCTCTGACG GGCGGACCGC	1020
ACCCCTTCACG GTGGTGGGGG CTGACCCCAC CAGTGATATC GCCGTCGTCC GTGTTCAGGG	1080
CGTCTCCGGG CTCACCCCGA TCTCCCTGGG TTCCTCCTCG GACCTGAGGG TCGGTCAGCC	1140
GGTGCTGGCG ATCGGGTCGC CGCTCGTTT GGAGGGCACC GTGACCACGG GGATCGTCAG	1200
CGCTCTCAAC CGTCCAGTGT CGACGACCGG CGAGGCCGGC AACCAGAACAA CCGTGCTGGA	1260
CGCCATTCAAG ACCGACGCCG CGATCAACCC CGGTAACCTCC GGGGGCGCGC TGGTGAACAT	1320
GAACGCTCAA CTCGTCGGAG TCAACTCGGC CATTGCCACG CTGGGCGCGG ACTCAGCCGA	1380
TGCGCAGAGC GGCTCGATCG GTCTCGTTT TGCGATTCCA GTCGACCAGG CCAAGCGCAT	1440
CGCCGACGAG TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAGGTGAC	1500
CAATGACAAA GACACCCCGG GCGCCAAGAT CGTCGAAGTA GTGGCCGGTG GTGCTGCCGC	1560
GAACGCTGGA GTGCCGAAGG GCGTCGTTGT CACCAAGGTC GACGACCGCC CGATCAACAG	1620
CGCGGACGCG TTGGTTGCCG CCGTGCGGTC CAAAGGCCCG GGCGCACGG TGGCGCTAAC	1680
CTTCAGGAT CCCTCGGGCG GTAGCCGCAC AGTGCAAGTC ACCCTCGGCA AGGCGGAGCA	1740
GATGAAGG TCGCCGCGCA GTGTTCAAAG C	1771

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1058 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTCCACCGCG GTGGCGGCCG CTCTAGAACT AGTGGATCCC CGGGCTGCA GGAATTCGGC	60
ACGAGGATCC GACGTCGCAG GTTGTGAAAC CGGCCGCCGC GGAAGTATCG GTCCATGCCT	120

AGCCC GGCGA CGGCGAGCGC CGGAATGGCG CGAGTGAGGA GGCGGGCAAT TTGGCGGGGC	180
CCGGCGACGG CGAGCGCCGG AATGGCGCGA GTGAGGGAGGC GGGCAGTCAT GCCCAGCGTG	240
ATCCAATCAA CCTGCATTG GCCTGCGGC CCATTTGACA ATCGAGGTAG TGAGCGCAA	300
TGAATGATGG AAAACGGCG GTGACGTCCG CTGTTCTGGT GGTGCTAGGT GCCTGCCTGG	360
CGTTGTGGCT ATCAGGATGT TCTTCGCCGA AACCTGATGC CGAGGAACAG GGTGTTCCCG	420
TGAGCCCGAC GGCGTCCGAC CCCGCGCTCC TCGCCGAGAT CAGGCAGTCG CTTGATGCGA	480
CAAAAGGGTT GACCAGCGTG CACGTAGCGG TCCGAACAAC CGGGAAAGTC GACAGCTTGC	540
TGGGTATTAC CAGTGCCGAT GTCGACGTCC GGGCCAATCC GCTCGCGGCA AAGGGCGTAT	600
GCACCTACAA CGACGAGCAG GGTGTCCCGT TTCGGGTACA AGGCGACAAC ATCTCGGTGA	660
AACTGTTCGA CGACTGGAGC AATCTCGGCT CGATTTCTGA ACTGTCAACT TCACGCGTGC	720
TCGATCCTGC CGCTGGGTG ACGCAGCTGC TGTCCGGTGT CACGAACCTC CAAGCGCAAG	780
GTACCGAAGT GATAGACGGA ATTCGACCA CCAAAATCAC CGGGACCATC CCCGCGAGCT	840
CTGTCAAGAT GCTTGATCCT GGCGCCAAGA GTGCAAGGCC GGCGACCGTG TGGATTGCC	900
AGGACGGCTC GCACCACCTC GTCCGAGCGA GCATCGACCT CGGATCCGGG TCGATTCA	960
TCACGCAGTC GAAATGGAAC GAACCCGTCA ACGTCGACTA GGCGAAGTT GCGTCGACGC	1020
GTTGNTCGAA ACGCCCTTGT GAACGGTGTC AACGGNAC	1058

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 542 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GAATTGGCA CGAGAGGTGA TCGACATCAT CGGGACCAGC CCCACATCCT GGGAACAGGC	60
GGCGGCGGAG GCGGTCCAGC GGGCGCGGGA TAGCGTCGAT GACATCCGCG TCGCTCGGGT	120
CATTGAGCAG GACATGGCCG TGGACAGCGC CGGCAAGATC ACCTACCGCA TCAAGCTCGA	180
AGTGTGTT AAGATGAGGC CGGCGCAACC GCGCTAGCAC GGGCCGGCGA GCAAGACGCA	240
AAATCGCACG GTTGCCTT GATTGCGCG ATTGTTGTC TGCTGCCGA GGCTTACCAAG	300
GCGCGGCCCA GGTCCGCGTG CTGCCGTATC CAGGCGTGCA TCGCGATTCC GGCGGCCACG	360
CCGGAGTTAA TGCTTCGCGT CGACCCGAAC TGGGCGATCC GCCGGNGAGC TGATCGATGA	420
CCGTGGCCAG CCCGTCGATG CCCGAGTTGC CCGAGGAAAC GTGCTGCCAG GCCGGTAGGA	480
AGCGTCCGTA GGCGGCGGTG CTGACCGGCT CTGCCTGCGC CCTCAGTGC GCGAGCGAGC	540
GG	542

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 913 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CGGTGCCGCC CGCGCCTCCG TTGCCCCAT TGCCGCCGTC GCCGATCAGC TGCGCATCGC	60
CACCATCACC GCCTTGCCG CCGGCACCGC CGGTGGCGCC GGGGCCGCCG ATGCCACCGC	120
TTGACCCCTGG CCGCCGGCGC CGCCATTGCC ATACAGCACC CCGCCGGGGG CACCGTTACC	180
GCCGTCGCCA CCGTCGCCGC CGCTGCCGTT TCAGGCCGGG GAGGCCGAAT GAACCGCCGC	240
CAAGCCCCGC GCCGGCACCG TTGCCGCCTT TTCCGCCCGC CCCGCCGGCG CCGCCAATTG	300

CCGAACAGCC	AMGCACCGTT	GCCGCCAGCC	CCGCCGCCGT	TAACGGCGCT	GCCGGGCGCC	360
GCCGCCGGAC	CGGCCATTAC	CGCCGTTCCC	GTTCGGTGCC	CCGCCGTTAC	CGGCCGCCGCC	420
GTTTGCCGCC	AATATTCGGC	GGGCACCGCC	AGACCCGCCG	GGGCCACCAT	TGCCGCCGGG	480
CACCGAAACA	ACAGCCCCAAC	GGTGCCGCCG	GCCCCGCCGT	TTGCCGCCAT	CACCGGCCAT	540
TCACCGCCAG	CACCGCCGTT	AATGTTTATG	AACCCGGTAC	CGCCAGCGCG	GCCCCTATTG	600
CCGGGCGCCG	GAGNGCGTGC	CCGCCGGCGC	CGCCAACGCC	CAAAGCCCG	GGGTTGCCAC	660
CGGCCCCGCC	GGACCCACCG	GTCCCGCCGA	TCCCCCCGTT	GCCGCCGGTG	CCGCCGCCAT	720
TGGTGCTGCT	GAAGCCGTTA	GCGCCGGTTC	CGCSGGTTCC	GGCGGTGGCG	CCNTGGCCGC	780
CGGCCCCGCC	GTTGCCGTAC	AGCCACCCCC	CGGTGGCGCC	GTTGCCGCCA	TTGCCGCCAT	840
TGCCGCCGTT	GCCGCCATTG	CCGCCGTTCC	CGCCGCCACC	GCCGGNTTGG	CCGCCGGCGC	900
CGCCGGCGGC	CGC					913

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1872 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GACTACGTTG	GTGTAGAAAA	ATCCTGCCGC	CCGGACCCCTT	AAGGCTGGGA	CAATTCTGA	60
TAGCTACCCC	GACACAGGAG	GTTACGGGAT	GAGCAATTG	CGCCGCCGCT	CACTCAGGTG	120
GTCATGGTTG	CTGAGCGTGC	TGGCTGCCGT	CGGGCTGGGC	CTGGCCACGG	CGCCGGCCCA	180
GGCGGCCCG	CCGGCCTTGT	CGCAGGACCG	GTTCGCCGAC	TTCCCCGGCG	TGCCCTCGA	240

CCCGTCCGCG ATGGTCGCC	AAGTGGGCC ACAGGTGGTC AACATCAACA CCAAAC	300
CTACAACAAAC GCCGTGGCG	CCGGGACCGG CATCGTCATC GATCCAACG GTGTCGTGCT	360
GACCAACAAAC CACGTGATCG	CGGGCGCCAC CGACATCAAT GCGTTCAGCG TCGGCTCCGG	420
CCAAACCTAC GGCGTCGATG	TGGTCGGGTA TGACCGCACCC CAGGATGTCG CGGTGCTGCA	480
GCTGCGCGGT GCCGGTGGCC	TGCCGTCGGC GGCGATCGGT GGCGGCGTCG CGGTTGGTGA	540
GCCC GTCGTC GCGATGGGCA	ACAGCGGTGG GCAGGGCGGA ACGCCCCGTG CGGTGCCTGG	600
CAGGGTGGTC GCGCTCGGCC	AAACCGTGCA GGCGTCGGAT TCGCTGACCG GTGCCGAAGA	660
GACATTGAAC GGGTTGATCC	AGTCGATGC CGCAATCCAG CCCGGTGATT CGGGCGGGCC	720
CGTCGTCAAC GGCGTAGGAC	AGGTGGTCGG TATGAACACG GCCGCGTCCG ATAACTTCCA	780
GCTGTCCAG GGTGGGCAGG	GATTGCCAT TCCGATCGGG CAGGCGATGG CGATCGCGGG	840
CCAAATCCGA TCAGGGTGGGG	GGTCACCCAC CGTTCATATC GGGCCTACCG CCTTCCTCGG	900
CTTGGGTGTT GTCGACAACA	ACGGCAACGG CGCACGAGTC CAACGCGTGG TCGGAAGCGC	960
TCCGGCGGCA AGTCTCGGCA	TCTCCACCAGG CGACGTGATC ACCGCGGTG ACGGCGCTCC	1020
GATCAACTCG GCCACCGCGA	TGGCGGACGC GCTTAACGGG CATCATCCCG GTGACGTCAT	1080
CTCGGTGAAC TGGCAAACCA	AGTCGGCGG CACGCGTACA GGGAACGTGA CATTGGCCGA	1140
GGGACCCCCCG GCCTGATTTG	TCGCGGATAC CACCCGCCGG CGGGCCAATT GGATTGGCGC	1200
CAGCCGTGAT TGCCGCGTGA	GCCCCCGAGT TCCGTCTCCC GTGCGCGTGG CATTGTGGAA	1260
GCAATGAACG AGGCAGAACAA	CAGCGTTGAG CACCCCTCCCG TGCAGGGCAG TTACGTCGAA	1320
GGCGGTGTGG TCGAGCATCC	GGATGCCAAG GACTTCGGCA GCGCCGCCGC CCTGCCCGCC	1380
GATCCGACCT GGTTTAAGCA	CGCCGTCTTC TACGAGGTGC TGGTCCGGGC GTTCTTGCAC	1440
GCCAGCGCGG ACGGTTCCGN	CGATCTGCGT GGACTCATCG ATGCCCTCGA CTACCTGCAG	1500
TGGCTTGGCA TCGACTGCAT	CTGTTGCCGC CGTTCTACG ACTCACCGCT GCGCGACGGC	1560
GGTTACGACA TTCGCGACTT	CTACAAGGTG CTGCCGAAT TCGGCACCGT CGACGATTTC	1620

GTCGCCCTGG TCGACACCGC TCACCGGCAG GGTATCCGCA TCATCACCGA CCTGGTGATG	1680
AATCACACCT CGGAGTCGCA CCCCTGGTTT CAGGAGTCCC GCCGCGACCC AGACGGACCG	1740
TACGGTGACT ATTACGTGTG GAGCGACACC AGCGAGCGCT ACACCGACGC CCGGATCATC	1800
TTCGTCGACA CCGAAGAGTC GAACTGGTCA TTGATCCTG TCCGCCGACA GTTNCTACTG	1860
GCACCGATTCTT	1872

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1482 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CTTCGCCGAA ACCTGATGCC GAGGAACAGG GTGTTCCCGT GAGCCCGACG GCGTCCGACC	60
CCGCGCTCCT CGCCGAGATC AGGCAGTCGC TTGATGCGAC AAAAGGGTTG ACCAGCGTGC	120
ACGTAGCGGT CCGAACAAACC GGGAAAGTCG ACAGCTTGCT GGGTATTACC AGTGCCGATG	180
TCGACGTCCG GGCCAATCCG CTCGCGGCAA AGGGCGTATG CACCTACAAC GACGAGCAGG	240
GTGTCCCGTT TCAGGTACAA GGCGACAACA TCTCGGTGAA ACTGTTCGAC GACTGGAGCA	300
ATCTCGGCTC GATTTCTGAA CTGTCAACTT CACGCGTGCT CGATCCTGCC GCTGGGGTGA	360
CGCAGCTGCT GTCCGGTGTC ACGAACCTCC AAGCGCAAGG TACCGAAGTG ATAGACGGAA	420
TTTCGACCAC CAAAATCACC GGGACCATCC CCGCGAGCTC TGTCAAGATG CTTGATCCTG	480
GCGCCAAGAG TGCAAGGCCG GCGACCGTGT GGATTGCCA GGACGGCTCG CACCACCTCG	540
TCCGAGCGAG CATCGACCTC GGATCCGGGT CGATTCAAGCT CACGCAGTCG AAATGGAACG	600

AACCCGTCAA CGTCGACTAG GCCGAAGTTG CGTCGACGCG TTGCTCGAAA CGCCCTTGTG	660
AACGGTGTCA ACGGCACCCG AAAACTGACC CCCTGACGGC ATCTGAAAAT TGACCCCCTA	720
GACCGGGCGG TTGGTGGTTA TTCTTCGGTG GTTCCGGCTG GTGGGACGCG GCCGAGGTCTG	780
CGGTCTTGA GCCGGTAGCT GTCGCCTTG AGGGCGACGA CTTCAGCATG GTGGACGAGG	840
CGGTCGATCA TGGCGGCAGC AACGACGTCG TCGCCGCCGA AAACCTCGCC CCACCGGCCG	900
AAGGCCTTAT TGGACGTGAC GATCAAGCTG GCCCGCTCAT ACCGGGAGGA CACCAGCTGG	960
AAGAAGAGGT TGGCGGCCTC GGGCTAAAC GGAATGTAAC CGACTTCGTC AACCAACCAGG	1020
AGCGGATAGC GGCCAAACCG GGTGAGTTCG GCGTAGATGC GCCCGGGCTG GTGAGCCTCG	1080
GCGAACCGTG CTACCCATTG GGCAGCGGTG GCGAACAGCA CCCGATGACC GGCTGACAC	1140
GCGCGTATCG CCAGGCCGAC CGCAAGATGA GTCTTCCCGG TGCCAGGCCG GGCCCAAAAA	1200
CACGACGTTA TCGCGGGCGG TGATGAAATC CAGGGTGCCC AGATGTGCGA TGGTGTGCG	1260
TTTGAGGCCA CGAGCATGCT CAAAGTCGAA CTCTTCCAAC GACTTCCGAA CGGGGAAGCG	1320
GGCGGCGCGG ATGCGGCCCT CACCACCATG GGACTCCCGG GCTGACACTT CCCGCTGCG	1380
GCAGGGCGCC AGGTATTCTT CGTGGCTCCA GTTCTCGCG CGGGCGCGAT CGGCCAGCCG	1440
GGACACTGAC TCACGCAGGG TGGGAGCTTT CAATGCTCTT GT	1482

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 876 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAATTCTGGCA CGAGCCGGCG ATAGCTTCTG GGCCGCGGCC GACCAGATGG CTCGAGGGTT

CGTGCTCGGG	GCCACCGCCG	GGCGCACCAAC	CCTGACCGGT	GAGGGCCTGC	AACACGCCGA	120
CGGTCACTCG	TGCTGCTGG	ACGCCACCAA	CCCGGCGGTG	GTTGCCTACG	ACCCGGCCTT	180
CGCCTACGAA	ATCGGCTACA	TCGNNGAAAG	CGGACTGGCC	AGGATGTGCG	GGGAGAACCC	240
GGAGAACATC	TTCTTCTACA	TCACCGTCTA	CAACGAGCCG	TACGTGCAGC	CGCCGGAGCC	300
GGAGAACCTTC	GATCCCGAGG	GCGTGCTGGG	GGGTATCTAC	CGNTATCACG	CGGCCACCAGA	360
GCAACGCACC	AACAAGGNGC	AGATCCTGGC	CTCCGGGGTA	GCGATGCCCG	CGGCGCTGCG	420
GGCAGCACAG	ATGCTGGCCG	CCGAGTGGGA	TGTCGCGGCC	GACGTGTGGT	CGGTGACCAG	480
TTGGGGCGAG	CTAAACCGCG	ACGGGGTGGT	CATCGAGACC	GAGAAGCTCC	GCCACCCCGA	540
TCGGCCGGCG	GGCGTGCCCT	ACGTGACGAG	AGCGCTGGAG	AATGCTCGGG	GCCCGGTGAT	600
CGCGGTGTCG	GACTGGATGC	GCGCGGTCCC	CGAGCAGATC	CGACCGTGGG	TGCCGGGCAC	660
ATACCTCACG	TTGGGCACCG	ACGGGTTCGG	TTTTCCGAC	ACTCGGCCCG	CCGGTCGTCG	720
TTACTTCAAC	ACCGACGCCG	AATCCCAGGT	TGGTCGCGGT	TTTGGGAGGG	GTTGGCCGGG	780
TCGACGGGTG	AATATCGACC	CATTGGTGC	CGGTCGTGGG	CCGCCCCCCC	AGTTACCCGG	840
ATTCGACGAA	GGTGGGGGGT	TGCGCCCGAN	TAAGTT			876

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1021 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

ATCCCCCCGG	GCTGCAGGAA	TTCGGCACGA	GAGACAAAAT	TCCACGCGTT	AATGCAGGAA	60
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CAGATTATA	ACGAATTAC	AGCGGCACAA	CAATATGTCG	CGATCGCGGT	TTATTTGAC	120
AGCGAAGACC	TGCCGCAGTT	GGCGAACCAT	TTTACAGCC	AAGCGGTCGA	GGAACGAAAC	180
CATGCAATGA	TGCTCGTGCA	ACACCTGCTC	GACCGCGACC	TTCGTGTCGA	AATTCCCGGC	240
GTAGACACGG	TGCGAAACCA	GTTCGACAGA	CCCCGCGAGG	CACTGGCGCT	GGCGCTCGAT	300
CAGGAACGCA	CAGTCACCGA	CCAGGTCGGT	CGGCTGACAG	CGGTGGCCCG	CGACGAGGGC	360
GATTTCTCG	GCGAGCAGTT	CATGCAGTGG	TTCTTGCGAGG	AACAGATCGA	AGAGGTGGCC	420
TTGATGGCAA	CCCTGGTGCG	GGTTGCCGAT	CGGGCCGGGG	CCAACCTGTT	CGAGCTAGAG	480
AACTTCGTCG	CACGTGAAGT	GGATGTGGCG	CCGGCCGCAT	CAGGCGCCCC	GCACGCTGCC	540
GGGGGCCGCC	TCTAGATCCC	TGGGGGGGAT	CAGCGAGTGG	TCCCCTTCGC	CCGCCCCGTCT	600
TCCAGCCAGG	CCTTGGTGCG	GCCGGGGTGG	TGAGTACCAA	TCCAGGCCAC	CCCGACCTCC	660
CGGNAAAAGT	CGATGTCCTC	GTACTCATCG	ACGTTCCAGG	AGTACACCGC	CCGGCCCTGA	720
GCTGCCGAGC	GGTCAACGAG	TTGCGGATAT	TCCTTTAACG	CAGGCAGTGA	GGGTCCCACG	780
GCGGTTGGCC	CGACCGCCGT	GGCCGCACTG	CTGGTCAGGT	ATCGGGGGGT	CTTGGCGAGC	840
AACAACGTCG	GCAGGGAGGGG	TGGAGCCCGC	CGGATCCGCA	GACCGGGGGG	GCGAAAACGA	900
CATCAACACC	GCACGGGATC	GATCTGCGGA	GGGGGGTGCG	GGAATACCGA	ACCGGTGTAG	960
GAGCGCCAGC	AGTTGTTTTT	CCACCAGCGA	AGCGTTTCG	GGTCATCGGN	GGCNNTTAAG	1020
T						1021

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 321 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CGTGCCGACG AACGGAAGAA CACAACCATG AAGATGGTGA AATCGATCGC CGCAGGTCTG	60
ACCGCCGCGG CTGCAATCGG CGCCGCTGCG GCCGGTGTGA CTTCGATCAT GGCTGGCGGN	120
CCGGTCGTAT ACCAGATGCA GCCGGTCGTC TTCCGGCGGC CACTGCCGTT GGACCCGGNA	180
TCCGCCCCCTG ANGTCCCGAC CGCCGCCAG TGGACCAGNC TGCTAACAG NCTCGNCGAT	240
CCCAACGTGT CGTTTNGAA CAAGGGNAGT CTGGTCGAGG GNNGNATCGG NGGNANGAG	300
GGNGNGNATC GNCGANCACA A	321

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 373 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TCTTATCGGT TCCGGTTGGC GACGGGTTTT GGGNGCGGGT GGTAAACCCG CTCGGCCAGC	60
CGATCGACGG GCGCGGAGAC GTCGACTCCG ATACTCGCG CGCGCTGGAG CTCCAGGCGC	120
CCTCGGTGGT GNACCGGCAA GGCGTGAAGG AGCCGTTGNA GACCGGGATC AAGGCGATTG	180
ACGCGATGAC CCCGATCGGC CGCGGGCAGC GCCAGCTGAT CATCGGGGAC CGCAAGACCG	240
GCAAAAACCG CCGTCTGTGT CGGACACCAT CCTCAAACCA GCGGGAAGAA CTGGGAGTCC	300
GGTGGATCCC AAGAACGAGG TCGCCTTGTG TATACGTTGG CCATCGGGCA AGAAGGGGAA	360
CTTACCATCG CCG	373

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 352 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

G TGACGCCGT GATGGGATT C TGGGCAGGG CCGGTCCGCT GGCGGTGGTG GATCAGCAAC	60
TGGTTACCCG GGTGCCGCAA GGCTGGTCGT TTGCTCAGGC AGCCGCTGTG CCGGTGGTGT	120
TCTTGACGGC CTGGTACGGG TTGGCCGATT TAGCCGAGAT CAAGGCGGGC GAATCGGTGC	180
TGATCCATGC CGGTACCGGC GGTGTGGCA TGGCGGCTGT GCAGCTGGCT CGCCAGTGGG	240
GCGTGGAGGT TTTCGTCACC GCCAGCCGTG GNAAGTGGGA CACGCTGCGC GCCATNGNGT	300
TTGACGACGA NCCATATCGG NGATTCCCNC ACATNCGAAG TTCCGANGGA GA	352

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 726 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GAAATCCGCG TTCATTCCGT TCGACCAGCG GCTGGCGATA ATCGACGAAG TGATCAAGCC	60
GCGGTTCGCG GCGCTCATGG GTCACAGCGA GTAATCAGCA AGTTCTCTGG TATATCGCAC	120
CTAGCGTCCA GTTGCTTGCC AGATCGCTT CGTACCGTCA TCGCATGTAC CGGTTCGCGT	180
GCCGCACGCT CATGCTGGCG GCGTGCATCC TGGCCACGGG TGTGGCGGGT CTCGGGGTCA	240

GCGCGCAGTC CGCAGCCAA ACCGCGCCGG TGCCCGACTA CTACTGGTGC CCGGGGCAGC	300
CTTTCGACCC CGCATGGGGG CCCAACTGGG ATCCCTACAC CTGCCATGAC GACTTCCACC	360
GCGACAGCGA CGGCCCGAC CACAGCCGCG ACTACCCCGG ACCCATCCTC GAAGGTCCCG	420
TGCTTGACGA TCCCAGGTGCT GCGCCGCCGC CCCCGGCTGC CGGTGGCGGC GCATAGCGCT	480
CGTTGACCGG GCCGCATCAG CGAATACGCG TATAAACCCG GGCGTGCCCC CGGCAAGCTA	540
CGACCCCCGG CGGGGCAGAT TTACGCTCCC GTGCCGATGG ATCGCGCCGT CCGATGACAG	600
AAAATAGGCG ACGGTTTG CAACCGCTTG GAGGACGCTT GAAGGGAACC TGTCAATGAAC	660
GGCGACAGCG CCTCCACCAT CGACATCGAC AAGGTTGTTA CCCGCACACC CGTTGCCGG	720
ATCGTG	726

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 580 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CGCGACGACG ACGAACGTCG GGCCCACCAAC CGCCTATGCG TTGATGCAGG CGACCGGGAT	60
GGTCGCCGAC CATATCCAAG CATGCTGGGT GCCCACTGAG CGACCTTTG ACCAGCCGGG	120
CTGCCCCATG GCGGCCCGGT GAAGTCATTG CGCCGGGGCT TGTGCACCTG ATGAACCCGA	180
ATAGGGAACA ATAGGGGGGT GATTTGGCAG TTCAATGTCG GGTATGGCTG GAAATCCAAT	240
GGCGGGGCAT GCTCGGCGCC GACCAGGCTC GCGCAGGCGG GCCAGCCGA ATCTGGAGGG	300
AGCACTCAAT GGCGCGATG AAGCCCCGGA CGGGCGACGG TCCTTGGAA GCAACTAAGG	360

AGGGGCGCGG CATTGTGATG CGAGTACCAAC TTGAGGGTGG CGGTCGCCTG GTCGTCGAGC	420
TGACACCCGA CGAACGCCGCC GCACTGGGTG ACGAACTCAA AGGC GTTACT AGCTAAGACC	480
AGCCCACCGG CGAATGGTCG GCGTTACGCG CACACCTTCC GGTAGATGTC CAGTGTCTGC	540
TCGGCGATGT ATGCCAGGA GAACTCTTGG ATACAGCGCT	580

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 160 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AACGGAGGCG CCGGGGGTTT TGGCGGGGCC GGGGCGGTG GCGGCAACGG CGGGGCCGGC	60
GGTACCGCCG GGTTGTTCGG TGTCGGCGGG GCCGGTGGGG CCGGAGGCAA CGGCATCGCC	120
GGTGTACCGG GTACGTCGGC CAGCACACCG GGTGGATCCG	160

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 272 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GACACCGATA CGATGGTGAT GTACGCCAAC GTTGTGACA CGCTCGAGGC GTTCACGATC	60
CAGCGCACAC CCGACGGCGT GACCATCGGC GATGCGGCC CGTTCGCGGA GGCGGCTGCC	120

AAGGCGATGG GAATCGACAA GCTGCAGGT ATTCAACCG GAATGGACCC CGTCGTCGCT	180
GAACGCGAAC AGTGGGACGA CGGCAACAAC ACGTTGGCGT TGGCGCCCGG TGTCGTTGTC	240
GCCTACGAGC GCAACGTACA GACCAACGCC CG	272

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 317 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GCAGCCGGTG GTTCTCGGAC TATCTGCGCA CGGTGACGCA GCGCGACGTG CGCGAGCTGA	60
AGCGGATCGA GCAGACGGAT CGCCTGCCGC GGTTCATGCG CTACCTGGCC GCTATCACCG	120
CGCAGGAGCT GAACGTGGCC GAAGCGGCGC GGGTCATCGG GGTCGACGCG GGGACGATCC	180
GTTCGGATCT GGCGTGGTTC GAGACGGTCT ATCTGGTACA TCGCCTGCC GCCTGGTCGC	240
GGAATCTGAC CGCGAAGATC AAGAAGCGGT CAAAGATCCA CGTCGTCGAC AGTGGCTTCG	300
CGGCCTGGTT GCGCGGG	317

(2) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 182 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GATCGTGGAG CTGTCGATGA ACAGCGTTGC CGGACGCGCG GCGGCCAGCA CGTCGGTGTA	60
GCAGCGCCGG ACCACCTCGC CGGTGGCAG CATGGTGATG ACCACGTCGG CCTCGGCCAC	120
CGCTTCGGGC GCGCTACGAA ACACCGCGAC ACCGTGCGCG GCGGCCGG ACGCCGCCGT	180
GG	182

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 308 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GATCGCGAAG TTTGGTGAGC AGGTGGTCGA CGCGAAAGTC TGGGCGCCTG CGAACGGGT	60
CGGCGTTCAC GAGGCGAAGA CACGCCGTGC CGAGCTGCTG CGGCTCGTCT ACGGCGGGCA	120
GAGGTTGAGA TTGCCCGCCG CGGCGAGCCG GTAGCAAAGC TTGTGCCGCT GCATCCTCAT	180
GAGACTCGGC GGTTAGGCAT TGACCATGGC GTGTACCGCG TGCCCGACGA TTTGGACGCT	240
CCGTTGTCAG ACGACGTGCT CGAACGCTTT CACCGGTGAA GCGCTACCTC ATCGACACCC	300
ACGTTTGG	308

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 267 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CCGACGACGA GCAACTCACG TGGATGATGG TCGGCAGCGG CATTGAGGAC GGAGAGAATC	60
CGGCCGAAGC TGCCGCGCGG CAAGTGCTCA TAGTGACCGG CCGTAGAGGG CTCCCCGAT	120
GGCACCGGAC TATTCTGGTG TGCCGCTGGC CGGTAAGAGC GGGTAAAAGA ATGTGAGGGG	180
ACACGATGAG CAATCACACC TACCGAGTGA TCGAGATCGT CGGGACCTCG CCCGACGGCG	240
TCGACGCGGC AATCCAGGGC GGTCTGG	267

(2) INFORMATION FOR SEQ ID NO:32:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 189 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CTCGTGCCGA AAGAATGTGA GGGGACACGA TGAGCAATCA CACCTACCGA GTGATCGAGA	60
TCGTCGGGAC CTCGCCCCAC GGCGTCGACG CGGCAATCCA GGGCGGTCTG GCCCGAGCTG	120
CGCAGACCAT GCGCGCGCTG GACTGGTCG AAGTACAGTC AATTGAGGC CACCTGGTCG	180
ACGGAGCGG	189

(2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 851 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CTGCAGGGTG GCGTGGATGA GCGTCACCGC GGGGCAGGCC GAGCTGACCG CCGCCCAGGT	60
CCGGGTTGCT GCGGCAGGCCT ACGAGACGGC GTATGGGCTG ACGGTGCCCG CGCCGGTGAT	120
CGCCGAGAAC CGTGCTGAAC TGATGATTCT GATAGCGACC AACCTTTGG GGCAAAACAC	180
CCCGGCGATC GCGGTCAACG AGGCCGAATA CGGCGAGATG TGGGCCAAG ACGCCGCCGC	240
GATGTTGGC TACGCCGCG CGACGGCGAC GGCGACGGCG ACGTTGCTGC CGTTGAGGA	300
GGCGCCGGAG ATGACCAGCG CGGGTGGCT CCTCGAGCAG GCCGCCGCGG TCGAGGAGGC	360
CTCCGACACC GCCGCGGCGA ACCAGTTGAT GAACAATGTG CCCCAGGCC TGAAACAGTT	420
GGCCCCAGCCC ACGCAGGGCA CCACGCCTTC TTCCAAGCTG GGTGGCTGT GGAAGACGGT	480
CTCGCCGCAT CGGTCGCCGA TCAGAACAT GGTGTCGATG GCCAACAAACC ACATGTCGAT	540
GACCAACTCG GGTGTGTCGA TGACCAACAC CTTGAGCTCG ATGTTGAAGG GCTTGCTCC	600
GGCGGCGGCC GCCCAGGCCG TGCAAACCGC GGCGCAAAAC GGGGTCCGGG CGATGAGCTC	660
GCTGGGCAGC TCGCTGGTT CTTCGGGTCT GGGCGGTGGG GTGGCCGCCA ACTTGGGTG	720
GGCGGCCTCG GTACGGTATG GTCACCGGGA TGGCGGAAAA TATGCANAGT CTGGTCGGCG	780
GAACGGTGGT CGGGCGTAAG GTTACCCCCC GTTTCTGGA TGCGGTGAAC TTCGTCAACG	840
GAAACAGTTA C	851

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 254 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GATCGATCGG GCGGAAATT	60
GGACCAGATT CGCCTCCGGC	
GATAACCAA TCAATCGAAC	
CTAGATTAT TCCGTCCAGG GGCCCGAGTA ATGGCTCGCA	120
GGAGAGGAAC CTTACTGCTG	
CGGGCACCTG TCGTAGGTCC TCGATACGGC GGAAGGCGTC	180
GACATTTCC ACCGACACCC	
CCATCCAAAC GTTCGAGGGC CACTCCAGCT TGTGAGCGAG	240
GCGACCCAGT CGCAGGCTGC	
GCTTGGTCAA GATC	254

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 408 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CGGCACGAGG ATCCTGACCG AAGCGGCCGC CGCCAAGGCG AAGTCGCTGT	60
TGGACCAGGA	
GGGACGGGAC GATCTGGCGC TGCGGATCGC GGTCAGCCG GGGGGGTGCG CTGGATTGCG	120
CTATAACCTT TTCTTCGACG ACCGGACGCT GGATGGTGAC CAAACCGCGG AGTCGGTGG	180
TGTCAGGTTG ATCGTGGACC GGATGAGCGC GCCGTATGTG GAAGGCGCGT CGATCGATT	240
CGTCGACACT ATTGAGAACG AAGGNTTCAC CATCGACAAT CCCAACGCCA CC GGCTCCTG	300
CGCGTGCAGG GATTGTTCA ACTGATAAAA CGCTAGTACG ACCCCGCGGT GCGAACACG	360
TACGAGCACA CCAAGACCTG ACCGCGCTGG AAAAGCAACT GAGCGATG	408

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 181 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GC GG TG CGG CG GAT CC GG C GGG T GG TT GA A CG GCA AC GG C GGG GCC CGG C GGG GCG CG	60
GG ACC CG GCG C TA AC GG TG GT G C C G GCG CA A CG C CT GG TT G T C G G G G C C G G G G T C C G	120
G C G G N G C C G G C ACC A AT GG T G G N G T C G G C G G G T C C G G C G G A C G G C G	180
G	181

(2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 290 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GC GG TG CGG CG GAT CC GG C GGG T GG TT GA A CG GCA AC GG C GGG T G C G G C G G G G C G	60
G C G A C G G C G T C T T G C C G G T G C C G G C G G C C A G G G C G G C C T C G G T G G G C A G G G C A A T G	120
G C G G C G G C T C A C C G G C G G C A A C G G C G G T C T T G G C G G C G C G G C G G T G G C G G A A C G	180
C C C C G G A C G G C G G C T T C G G T G G C A A C G G C G G C G G C G G C G G C G G C G G C G G C G G C G G C G	240
G C A C T C A G A G C G C G A C C G G C C T C G G N G G T G A C G G C G G T G A C G G C G G T G A C	290

(2) INFORMATION FOR SEQ ID NO:38:

- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 34 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GATCCAGTGG CATGGNGGGT GTCAGTGGAA GCAT

34

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 155 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GATCGCTGCT CGTCCCCCCC TTGCCGCCGA CGCCACCGGT CCCACCGTTA CCGAACAAAGC

60

TGGCGTGTC GCCAGCACCC CCGGCACCGC CGACGCCGGA GTCGAACAAT GGCACCGTCG

120

TATCCCCACC ATTGCCGCCG GNCCCACCGG CACCG

155

(2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 53 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

ATGGCGTTCA CGGGGCGCCG GGGACCGGGC AGCCCGGNGG GGCCGGGGGG TGG 53

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GATCCACCGC GGGTGCAGAC GGTGCCCGCG GCGCCACCCC GACCAGCGGC GGCAACGGCG 60

GCACCGGGCGG CAACGGCGCG AACGCCACCG TCGTCGGNGG GGCCGGGGGG GCCGGCGGCA 120

AGGGCGGCAA CG 132

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GATCGGCGGC CGGNACGGNC GGGGACGGCG GCAAGGGCGG NAACGGGGC GCCGNAGCCA 60

CCNGCCAAGA ATCCTCCGNG TCCNCCAATG GCGCGAATGG CGGACAGGGC GGCAACGGCG 120

GCANCGGCGG CA 132

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 702 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CGGCACGAGG ATCGGTACCC CGCGGCATCG GCAGCTGCCG ATTGCCGGG TTTCCCCACC	60
CGAGGAAAGC CGCTACCAGA TGGCGCTGCC GAAGTAGGGC GATCCGTTCG CGATGCCGGC	120
ATGAACGGGC GGCATCAAAT TAGTGCAGGA ACCTTCAGT TTAGCGACGA TAATGGCTAT	180
AGCACTAAGG AGGATGATCC GATATGACGC AGTCGCAGAC CGTGACGGTG GATCAGCAAG	240
AGATTTGAA CAGGGCCAAC GAGGTGGAGG CCCCAGATGGC GGACCCACCG ACTGATGTCC	300
CCATCACACC GTGCGAACTC ACGGNGGNNTA AAAACGCCGC CCAACAGNTG GTNTTGTCCG	360
CCGACAACAT GCGGGAATAC CTGGCGGCCG GTGCCAAAGA GCGGCAGCGT CTGGCGACCT	420
CGCTGCGCAA CGCGGCCAAG GNGTATGGCG AGGTTGATGA GGAGGCTGCG ACCGCGCTGG	480
ACAACGACGG CGAAGGAACT GTGCAGGCAG AATCGGCCGG GGCGTCGGA GGGGACAGTT	540
CGGCCGAACT AACCGATACT CCGAGGGTGG CCACGGCCGG TGAACCCAAC TTCATGGATC	600
TCAAAGAAGC GGCAAGGAAG CTCGAAACGG GCGACCAAGG CGCATCGCTC GCGCACTGNG	660
GGGATGGGTG GAACACTTNC ACCCTGACGC TGCAAGGCGA CG	702

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 298 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GAAGCCGCAG CGCTGTCGGG CGACGTGGCG GTCAAAGCGG CATCGCTCGG TGGCGGTGGA	60
GGCGGCGGGG TGCCGTCGGC GCCGTTGGGA TCCGCGATCG GGGGCGCCGA ATCGGTGCGG	120
CCCGCTGGCG CTGGTGACAT TGCCGGCTTA GGCCAGGGAA GGGCCGGCGG CGGCGCCGCG	180
CTGGGCGGCG GTGGCATGGG AATGCCGATG GGTGCCGCGC ATCAGGGACA AGGGGGCGCC	240
AAGTCCAAGG GTTCTCAGCA GGAAGACGAG GCGCTCTACA CCGAGGATCC TCGTGCG	298

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1058 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CGGCACGAGG ATCGAATCGC GTGCCGGGA GCACAGCGTC GCACTGCACC AGTGGAGGAG	60
CCATGACCTA CTCGCCGGGT AACCCCGGAT ACCCGCAAGC GCAGCCCGCA GGCTCCTACG	120
GAGGCACAC ACCCTCGTTC GCCCACGCG ATGAGGGTGC GAGCAAGCTA CCGATGTACC	180
TGAACATCGC GGTGGCAGTG CTCGGTCTGG CTGCGTACTT CGCCAGCTTC GGCCAATGT	240
TCACCCCTCAG TACCGAACTC GGGGGGGGTG ATGGCGCAGT GTCCGGTGAC ACTGGGCTGC	300
CGGTGGGGGT GGCTCTGCTG GCTGCGCTGC TTGCCGGGT GGTTCTGGTG CCTAAGGCCA	360
AGAGCCATGT GACGGTAGTT GCGGTGCTCG GGGTACTCGG CGTATTTCTG ATGGTCTCGG	420

CGACGTTAA CAAGCCCAGC GCCTATTGA CCGGTTGGGC ATTGTGGT GTGTTGGCTT	480
TCATCGTGTT CCAGGCGGTT GCGGCAGTCC TGGCGCTCTT GGTGGAGACC GGCCTATCA	540
CCGCGCCGGC GCCGCGGCC AAGTCGACC CGTATGGACA GTACGGCGG TACGGGCAGT	600
ACGGGCAGTA CGGGGTGCAG CGGGGTGGGT ACTACGGTCA GCAGGGTGCT CAGCAGGCCG	660
CGGGACTGCA GTCGCCCGGC CCGCAGCAGT CTCCGCAGCC TCCCAGGATAT GGGTCGCAGT	720
ACGGCGGCTA TTCTGTCAGT CCGAGCCAAT CGGGCAGTGG ATACACTGCT CAGCCCCCGG	780
CCCAGCCGCC GGCGCAGTCC GGGTCGCAAC AATCGCACCA GGGCCCATCC ACGCCACCTA	840
CCGGCTTCC GAGCTTCAGC CCACCACCCAC CGGTCAGTGC CGGGACGGGG TCGCAGGCTG	900
GTTGGCTCC AGTCAACTAT TCAAACCCCA GCGGGGGCGA GCAGTCGTCG TCCCCGGGG	960
GGGCGCCGGT CTAACCGGGC GTTCCCGCGT CCGGTCGCGC GTGTGCGCGA AGAGTGAACA	1020
GGGTGTCAGC AAGCGCGGAC GATCCTCGTG CCGAATTG	1058

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 327 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CGGCACGAGA GACCGATGCC GCTACCCCTCG CGCAGGAGGC AGGTAATTC GAGCGGATCT	60
CCGGCGACCT GAAAACCCAG ATCGACCAGG TGGAGTCGAC GGCAGGTTCG TTGCAGGGCC	120
AGTGGCGCGG CGCGGCGGGG ACGGCCGCC AGGCCGCGGT GGTGCGCTTC CAAGAACGAG	180
CCAATAAGCA GAAGCAGGAA CTCGACGAGA TCTCGACGAA TATTCGTCA GCGGGCGTCC	240
AATACTCGAG GGCGACGAG GAGCAGCAGC AGGCAGCTGTC CTCGCAAATG GGCTCTGAC	300

CCGCTAATAC GAAAAGAAAC GGAGCAA 327

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CGGTCGCGAT GATGGCGTTG TCGAACGTGA CCGATTCTGT ACCGCCGTCG TTGAGATCAA 60

CCAACAACGT GTTGGCGTCG GCAAATGTGC CGNACCCGTG GATCTCGGTG ATCTTGTCT 120

TCTTCATCAG GAAGTGCACA CGGGCCACCC TGCCCTCGGN TACCTTCGG 170

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 127 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GATCCGGCGG CACGGGGGGT GCCGGCGGCA GCACCGCTGG CGCTGGCGGC AACGGCGGGG 60

CCGGGGGGTGG CGGCGGAACC GGTGGGTTGC TCTTCGGCAA CGGCGGTGCC GGCGGGCACG 120

GGGCCGT 127

(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 81 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CGGCGGGCAAG GGCGGCACCG CGGGCAACGG GAGCGGCGCG GCCGGCGGCA ACGGCGGCAA 60
CGGCGGCTCC GGCCTCAACG G 81

(2) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 149 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GATCAGGGCT GGCCGGCTCC GGCCAGAAGG GCGGTAACGG AGGAGCTGCC GGATTGTTT 60
GCAACGGCGG GGCCGGNGGT GCCGGCGCGT CCAACCAAGC CGGTAACGGC GGNGCCGGCG 120
GAAACGGTGG TGCCGGTGGG CTGATCTGG 149

(2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 355 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CGGCACGAGA TCACACCTAC CGAGTGATCG AGATCGTCGG GACCTCGCCC GACGGTGTG	60
ACGCGGNAAT CCAGGGCGGT CTGGCCCGAG CTGCGCAGAC CATGCGCGCG CTGGACTGGT	120
TCGAAGTACA GTCAATTGA GGCCACCTGG TCGACGGAGC GGTCGCGCAC TTCCAGGTGA	180
CTATGAAAGT CGGCTTCCGC CTGGAGGATT CCTGAACCTT CAAGCGCGGC CGATAACTGA	240
GGTGCATCAT TAAGCGACTT TTCCAGAACCA TCCTGACGCG CTCGAAACGC GGTTCAGCCG	300
ACGGTGGCTC CGCCGAGGCG CTGCCTCAA AATCCCTGCG ACAATTGTC GGC	355

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 999 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ATGCATCACC ATCACCATCA CATGCATCAG GTGGACCCA ACTTGACACG TCGCAAGGGA	60
CGATTGGCGG CACTGGCTAT CGCGGCGATG GCCAGCGCCA GCCTGGTGAC CGTTGCGGTG	120
CCCGCGACCG CCAACGCCGA TCCGGAGCCA GCGCCCCCGG TACCCACAAC GGCCGCCTCG	180
CCGCCGTCGA CCGCTGCAGC GCCACCCGCA CCGGCGACAC CTGTTGCCCG CCCACCACCG	240
GCCGCCGCCA ACACGCCGAA TGCCCAGCCG GGCGATCCCA ACGCAGCACC TCCGCCGGCC	300
GACCCGAACG CACCGCCGCC ACCTGTCATT GCCCCAAACG CACCCCAACC TGTCCGGATC	360
GACAACCCGG TTGGAGGATT CAGCTTCGCG CTGCCTGCTG GCTGGGTGGA GTCTGACGCC	420

GCCCACCTTCG	ACTACGGTTC	AGCACTCCTC	AGCAAAACCA	CCGGGGACCC	GCCATTTCCC	480
GGACAGCCGC	CGCCGGTGGC	CAATGACACC	CGTATCGTGC	TCGGCCGGCT	AGACCAAAAG	540
CTTTACGCCA	GCGCCGAAGC	CACCGACTCC	AAGGCCGCGG	CCCGGTTGGG	CTCGGACATG	600
GGTGAGTTCT	ATATGCCCTA	CCCGGGCACC	CGGATCAACC	AGGAAACCGT	CTCGCTCGAC	660
GCCAACGGGG	TGTCTGGAAG	CGCGTCGTAT	TACGAAGTCA	AGTTCAGCGA	TCCGAGTAAG	720
CCGAACGGCC	AGATCTGGAC	GGGCGTAATC	GGCTCGCCCG	CGGCGAACGC	ACCGGACGCC	780
GGGCCCCCTC	AGCGCTGGTT	TGTGGTATGG	CTCGGGACCG	CCAACAACCC	GGTGGACAAG	840
GGCGCGGCCA	AGGCGCTGGC	CGAATCGATC	CGGCCTTGG	TCGCCCCGCC	GCCGGCGCCG	900
GCACCGGCTC	CTGCAGAGCC	CGCTCCGGCG	CCGGCGCCGG	CCGGGGAAAGT	CGCTCCTACC	960
CCGACGACAC	CGACACCGCA	GC GGACCTTA	CCGGCCTGA			999

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- SEQUENCE CHARACTERISTICS:

 - (A) LENGTH: 332 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Met His His His His His Met His Gln Val Asp Pro Asn Leu Thr
1 5 10 15

Arg Arg Lys Gly Arg Leu Ala Ala Leu Ala Ile Ala Ala Met Ala Ser
20 25 30

Ala Ser Leu Val Thr Val Ala Val Pro Ala Thr Ala Asn Ala Asp Pro
35 40 45

Glu Pro Ala Pro Pro Val Pro Thr Thr Ala Ala Ser Pro Pro Ser Thr
50 55 60

Ala Ala Ala Pro Pro Ala Pro Ala Thr Pro Val Ala Pro Pro Pro Pro
65 70 75 80

Ala Ala Ala Asn Thr Pro Asn Ala Gln Pro Gly Asp Pro Asn Ala Ala
85 90 95

Pro Pro Pro Ala Asp Pro Asn Ala Pro Pro Pro Pro Val Ile Ala Pro
100 105 110

Asn Ala Pro Gln Pro Val Arg Ile Asp Asn Pro Val Gly Gly Phe Ser
115 120 125

Phe Ala Leu Pro Ala Gly Trp Val Glu Ser Asp Ala Ala His Phe Asp
130 135 140

Tyr Gly Ser Ala Leu Leu Ser Lys Thr Thr Gly Asp Pro Pro Phe Pro
145 150 155 160

Gly Gln Pro Pro Pro Val Ala Asn Asp Thr Arg Ile Val Leu Gly Arg
165 170 175

Leu Asp Gln Lys Leu Tyr Ala Ser Ala Glu Ala Thr Asp Ser Lys Ala
180 185 190

Ala Ala Arg Leu Gly Ser Asp Met Gly Glu Phe Tyr Met Pro Tyr Pro
195 200 205

Gly Thr Arg Ile Asn Gln Glu Thr Val Ser Leu Asp Ala Asn Gly Val
210 215 220

Ser Gly Ser Ala Ser Tyr Tyr Glu Val Lys Phe Ser Asp Pro Ser Lys
225 230 235 240

Pro Asn Gly Gln Ile Trp Thr Gly Val Ile Gly Ser Pro Ala Ala Asn
245 250 255

Ala Pro Asp Ala Gly Pro Pro Gln Arg Trp Phe Val Val Trp Leu Gly
260 265 270

Thr Ala Asn Asn Pro Val Asp Lys Gly Ala Ala Lys Ala Leu Ala Glu
275 280 285

Ser Ile Arg Pro Leu Val Ala Pro Pro Pro Ala Pro Ala Pro Ala Pro
290 295 300

Ala Glu Pro Ala Pro Ala Pro Ala Pro Ala Gly Glu Val Ala Pro Thr
305 310 315 320
Pro Thr Thr Pro Thr Pro Gln Arg Thr Leu Pro Ala
325 330

(2) INFORMATION FOR SEQ ID NO:54:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Asp Pro Val Asp Ala Val Ile Asn Thr Thr Xaa Asn Tyr Gly Gln Val
1 5 10 15

Val Ala Ala Leu
20

(2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Ala Val Glu Ser Gly Met Leu Ala Leu Gly Thr Pro Ala Pro Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Ala	Ala	Met	Lys	Pro	Arg	Thr	Gly	Asp	Gly	Pro	Leu	Glu	Ala	Ala	Lys
1				5					10					15	
Glu Gly Arg															

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Tyr	Tyr	Trp	Cys	Pro	Gly	Gln	Pro	Phe	Asp	Pro	Ala	Trp	Gly	Pro
1				5					10				15	

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Asp Ile Gly Ser Glu Ser Thr Glu Asp Gln Gln Xaa Ala Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Ala Glu Glu Ser Ile Ser Thr Xaa Glu Xaa Ile Val Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Asp Pro Glu Pro Ala Pro Pro Val Pro Thr Ala Ala Ala Ala Pro Pro
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Ala	Pro	Lys	Thr	Tyr	Xaa	Glu	Glu	Leu	Lys	Gly	Thr	Asp	Thr	Gly
1					5				10					15

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln	Gln	Thr	Ser
1					5				10					15	

Leu	Leu	Asn	Asn	Leu	Ala	Asp	Pro	Asp	Val	Ser	Phe	Ala	Asp		
					20				25				30		

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 187 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Thr Gly Ser Leu Asn Gln Thr His Asn Arg Arg Ala Asn Glu Arg Lys
1 5 10 15

Asn Thr Thr Met Lys Met Val Lys Ser Ile Ala Ala Gly Leu Thr Ala
20 25 30

Ala Ala Ala Ile Gly Ala Ala Ala Gly Val Thr Ser Ile Met Ala
35 40 45

Gly Gly Pro Val Val Tyr Gln Met Gln Pro Val Val Phe Gly Ala Pro
50 55 60

Leu Pro Leu Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln
65 70 75 80

Leu Thr Ser Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala
85 90 95

Asn Lys Gly Ser Leu Val Glu Gly Gly Ile Gly Gly Thr Glu Ala Arg
100 105 110

Ile Ala Asp His Lys Leu Lys Lys Ala Ala Glu His Gly Asp Leu Pro
115 120 125

Leu Ser Phe Ser Val Thr Asn Ile Gln Pro Ala Ala Ala Gly Ser Ala
130 135 140

Thr Ala Asp Val Ser Val Ser Gly Pro Lys Leu Ser Ser Pro Val Thr
145 150 155 160

Gln Asn Val Thr Phe Val Asn Gln Gly Gly Trp Met Leu Ser Arg Ala
165 170 175

Ser Ala Met Glu Leu Leu Gln Ala Ala Gly Xaa
180 185

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 148 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Asp Glu Val Thr Val Glu Thr Thr Ser Val Phe Arg Ala Asp Phe Leu
1 5 10 15

Ser Glu Leu Asp Ala Pro Ala Gln Ala Gly Thr Glu Ser Ala Val Ser
20 25 30

Gly Val Glu Gly Leu Pro Pro Gly Ser Ala Leu Leu Val Val Lys Arg
35 40 45

Gly Pro Asn Ala Gly Ser Arg Phe Leu Leu Asp Gln Ala Ile Thr Ser
50 55 60

Ala Gly Arg His Pro Asp Ser Asp Ile Phe Leu Asp Asp Val Thr Val
65 70 75 80

Ser Arg Arg His Ala Glu Phe Arg Leu Glu Asn Asn Glu Phe Asn Val
85 90 95

Val Asp Val Gly Ser Leu Asn Gly Thr Tyr Val Asn Arg Glu Pro Val
100 105 110

Asp Ser Ala Val Leu Ala Asn Gly Asp Glu Val Gln Ile Gly Lys Leu
115 120 125

Arg Leu Val Phe Leu Thr Gly Pro Lys Gln Gly Glu Asp Asp Gly Ser
130 135 140

Thr Gly Gly Pro
145

(2) INFORMATION FOR SEQ ID NO:65:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 230 amino acids

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Thr Ser Asn Arg Pro Ala Arg Arg Gly Arg Arg Ala Pro Arg Asp Thr
1 5 10 15

Gly Pro Asp Arg Ser Ala Ser Leu Ser Leu Val Arg His Arg Arg Gln
20 25 30

Gln Arg Asp Ala Leu Cys Leu Ser Ser Thr Gln Ile Ser Arg Gln Ser
35 40 45

Asn Leu Pro Pro Ala Ala Gly Gly Ala Ala Asn Tyr Ser Arg Arg Asn
50 55 60

Phe Asp Val Arg Ile Lys Ile Phe Met Leu Val Thr Ala Val Val Leu
65 70 75 80

Leu Cys Cys Ser Gly Val Ala Thr Ala Ala Pro Lys Thr Tyr Cys Glu
85 90 95

Glu Leu Lys Gly Thr Asp Thr Gly Gln Ala Cys Gln Ile Gln Met Ser
100 105 110

Asp Pro Ala Tyr Asn Ile Asn Ile Ser Leu Pro Ser Tyr Tyr Pro Asp
115 120 125

Gln Lys Ser Leu Glu Asn Tyr Ile Ala Gln Thr Arg Asp Lys Phe Leu
130 135 140

Ser Ala Ala Thr Ser Ser Thr Pro Arg Glu Ala Pro Tyr Glu Leu Asn
145 150 155 160

Ile Thr Ser Ala Thr Tyr Gln Ser Ala Ile Pro Pro Arg Gly Thr Gln
165 170 175

Ala Val Val Leu Xaa Val Tyr His Asn Ala Gly Gly Thr His Pro Thr
180 185 190

Thr Thr Tyr Lys Ala Phe Asp Trp Asp Gln Ala Tyr Arg Lys Pro Ile
195 200 205

Thr Tyr Asp Thr Leu Trp Gln Ala Asp Thr Asp Pro Leu Pro Val Val
210 215 220

Phe Pro Ile Val Ala Arg
225 230

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1 5 10 15

Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
20 25 30

Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
35 40 45

Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
50 55 60

Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
65 70 75 80

Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
85 90 95

Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
100 105 110

Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
115 120 125
Gly Pro Pro Ala
130

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Val Pro Leu Arg Ser Pro Ser Met Ser Pro Ser Lys Cys Leu Ala Ala
1 5 10 15

Ala Gln Arg Asn Pro Val Ile Arg Arg Arg Arg Leu Ser Asn Pro Pro
20 25 30

Pro Arg Lys Tyr Arg Ser Met Pro Ser Pro Ala Thr Ala Ser Ala Gly
35 40 45

Met Ala Arg Val Arg Arg Arg Ala Ile Trp Arg Gly Pro Ala Thr Xaa
50 55 60

Ser Ala Gly Met Ala Arg Val Arg Arg Trp Xaa Val Met Pro Xaa Val
65 70 75 80

Ile Gln Ser Thr Xaa Ile Arg Xaa Xaa Gly Pro Phe Asp Asn Arg Gly
85 90 95

Ser Glu Arg Lys
100

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 163 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Met Thr Asp Asp Ile Leu Leu Ile Asp Thr Asp Glu Arg Val Arg Thr
1 5 10 15

Leu Thr Leu Asn Arg Pro Gln Ser Arg Asn Ala Leu Ser Ala Ala Leu
20 25 30

Arg Asp Arg Phe Phe Ala Xaa Leu Xaa Asp Ala Glu Xaa Asp Asp Asp
35 40 45

Ile Asp Val Val Ile Leu Thr Gly Ala Asp Pro Val Phe Cys Ala Gly
50 55 60

Leu Asp Leu Lys Val Ala Gly Arg Ala Asp Arg Ala Ala Gly His Leu
65 70 75 80

Thr Ala Val Gly Gly His Asp Gln Ala Gly Asp Arg Arg Asp Gln Arg
85 90 95

Arg Arg Gly His Arg Arg Ala Arg Thr Gly Ala Val Leu Arg His Pro
100 105 110

Asp Arg Leu Arg Ala Arg Pro Leu Arg Arg His Pro Arg Pro Gly Gly
115 120 125

Ala Ala Ala His Leu Gly Thr Gln Cys Val Leu Ala Ala Lys Gly Arg
130 135 140

His Arg Xaa Gly Pro Val Asp Glu Pro Asp Arg Arg Leu Pro Val Arg
145 150 155 160

Asp Arg Arg

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 344 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Met Lys Phe Val Asn His Ile Glu Pro Val Ala Pro Arg Arg Ala Gly
1 5 10 15

Gly Ala Val Ala Glu Val Tyr Ala Glu Ala Arg Arg Glu Phe Gly Arg
20 25 30

Leu Pro Glu Pro Leu Ala Met Leu Ser Pro Asp Glu Gly Leu Leu Thr
35 40 45

Ala Gly Trp Ala Thr Leu Arg Glu Thr Leu Leu Val Gly Gln Val Pro
50 55 60

Arg Gly Arg Lys Glu Ala Val Ala Ala Val Ala Ala Ser Leu Arg
65 70 75 80

Cys Pro Trp Cys Val Asp Ala His Thr Thr Met Leu Tyr Ala Ala Gly
85 90 95

Gln Thr Asp Thr Ala Ala Ala Ile Leu Ala Gly Thr Ala Pro Ala Ala
100 105 110

Gly Asp Pro Asn Ala Pro Tyr Val Ala Trp Ala Ala Gly Thr Gly Thr
115 120 125

Pro Ala Gly Pro Pro Ala Pro Phe Gly Pro Asp Val Ala Ala Glu Tyr
130 135 140

Leu Gly Thr Ala Val Gln Phe His Phe Ile Ala Arg Leu Val Leu Val
145 150 155 160

Leu Leu Asp Glu Thr Phe Leu Pro Gly Gly Pro Arg Ala Gln Gln Leu
165 170 175

100

Met Arg Arg Ala Gly Gly Leu Val Phe Ala Arg Lys Val Arg Ala Glu
180 185 190

His Arg Pro Gly Arg Ser Thr Arg Arg Leu Glu Pro Arg Thr Leu Pro
195 200 205

Asp Asp Leu Ala Trp Ala Thr Pro Ser Glu Pro Ile Ala Thr Ala Phe
210 215 220

Ala Ala Leu Ser His His Leu Asp Thr Ala Pro His Leu Pro Pro Pro
225 230 235 240

Thr Arg Gln Val Val Arg Arg Val Val Gly Ser Trp His Gly Glu Pro
245 250 255

Met Pro Met Ser Ser Arg Trp Thr Asn Glu His Thr Ala Glu Leu Pro
260 265 270

Ala Asp Leu His Ala Pro Thr Arg Leu Ala Leu Leu Thr Gly Leu Ala
275 280 285

Pro His Gln Val Thr Asp Asp Asp Val Ala Ala Ala Arg Ser Leu Leu
290 295 300

Asp Thr Asp Ala Ala Leu Val Gly Ala Leu Ala Trp Ala Ala Phe Thr
305 310 315 320

Ala Ala Arg Arg Ile Gly Thr Trp Ile Gly Ala Ala Ala Glu Gly Gln
325 330 335

Val Ser Arg Gln Asn Pro Thr Gly
340

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 485 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Asp Asp Pro Asp Met Pro Gly Thr Val Ala Lys Ala Val Ala Asp Ala
1 5 10 15

Leu Gly Arg Gly Ile Ala Pro Val Glu Asp Ile Gln Asp Cys Val Glu
20 25 30

Ala Arg Leu Gly Glu Ala Gly Leu Asp Asp Val Ala Arg Val Tyr Ile
35 40 45

Ile Tyr Arg Gln Arg Arg Ala Glu Leu Arg Thr Ala Lys Ala Leu Leu
50 55 60

Gly Val Arg Asp Glu Leu Lys Leu Ser Leu Ala Ala Val Thr Val Leu
65 70 75 80

Arg Glu Arg Tyr Leu Leu His Asp Glu Gln Gly Arg Pro Ala Glu Ser
85 90 95

Thr Gly Glu Leu Met Asp Arg Ser Ala Arg Cys Val Ala Ala Glu
100 105 110

Asp Gln Tyr Glu Pro Gly Ser Ser Arg Arg Trp Ala Glu Arg Phe Ala
115 120 125

Thr Leu Leu Arg Asn Leu Glu Phe Leu Pro Asn Ser Pro Thr Leu Met
130 135 140

Asn Ser Gly Thr Asp Leu Gly Leu Leu Ala Gly Cys Phe Val Leu Pro
145 150 155 160

Ile Glu Asp Ser Leu Gln Ser Ile Phe Ala Thr Leu Gly Gln Ala Ala
165 170 175

Glu Leu Gln Arg Ala Gly Gly Thr Gly Tyr Ala Phe Ser His Leu
180 185 190

Arg Pro Ala Gly Asp Arg Val Ala Ser Thr Gly Gly Thr Ala Ser Gly
195 200 205

Pro Val Ser Phe Leu Arg Leu Tyr Asp Ser Ala Ala Gly Val Val Ser
210 215 220

102

Met Gly Gly Arg Arg Arg Gly Ala Cys Met Ala Val Leu Asp Val Ser
225 230 235 240

His Pro Asp Ile Cys Asp Phe Val Thr Ala Lys Ala Glu Ser Pro Ser
245 250 255

Glu Leu Pro His Phe Asn Leu Ser Val Gly Val Thr Asp Ala Phe Leu
260 265 270

Arg Ala Val Glu Arg Asn Gly Leu His Arg Leu Val Asn Pro Arg Thr
275 280 285

Gly Lys Ile Val Ala Arg Met Pro Ala Ala Glu Leu Phe Asp Ala Ile
290 295 300

Cys Lys Ala Ala His Ala Gly Gly Asp Pro Gly Leu Val Phe Leu Asp
305 310 315 320

Thr Ile Asn Arg Ala Asn Pro Val Pro Gly Arg Gly Arg Ile Glu Ala
325 330 335

Thr Asn Pro Cys Gly Glu Val Pro Leu Leu Pro Tyr Glu Ser Cys Asn
340 345 350

Leu Gly Ser Ile Asn Leu Ala Arg Met Leu Ala Asp Gly Arg Val Asp
355 360 365

Trp Asp Arg Leu Glu Glu Val Ala Gly Val Ala Val Arg Phe Leu Asp
370 375 380

Asp Val Ile Asp Val Ser Arg Tyr Pro Phe Pro Glu Leu Gly Glu Ala
385 390 395 400

Ala Arg Ala Thr Arg Lys Ile Gly Leu Gly Val Met Gly Leu Ala Glu
405 410 415

Leu Leu Ala Ala Leu Gly Ile Pro Tyr Asp Ser Glu Glu Ala Val Arg
420 425 430

Leu Ala Thr Arg Leu Met Arg Arg Ile Gln Gln Ala Ala His Thr Ala
435 440 445

Ser Arg Arg Leu Ala Glu Glu Arg Gly Ala Phe Pro Ala Phe Thr Asp
450 455 460

103

Ser Arg Phe Ala Arg Ser Gly Pro Arg Arg Asn Ala Gln Val Thr Ser
465 470 475 480

Val Ala Pro Thr Gly
485

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 267 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Gly Val Ile Val Leu Asp Leu Glu Pro Arg Gly Pro Leu Pro Thr Glu
1 5 10 15

Ile Tyr Trp Arg Arg Arg Gly Leu Ala Leu Gly Ile Ala Val Val Val
20 25 30

Val Gly Ile Ala Val Ala Ile Val Ile Ala Phe Val Asp Ser Ser Ala
35 40 45

Gly Ala Lys Pro Val Ser Ala Asp Lys Pro Ala Ser Ala Gln Ser His
50 55 60

Pro Gly Ser Pro Ala Pro Gln Ala Pro Gln Pro Ala Gly Gln Thr Glu
65 70 75 80

Gly Asn Ala Ala Ala Ala Pro Pro Gln Gly Gln Asn Pro Glu Thr Pro
85 90 95

Thr Pro Thr Ala Ala Val Gln Pro Pro Pro Val Leu Lys Glu Gly Asp
100 105 110

Asp Cys Pro Asp Ser Thr Leu Ala Val Lys Gly Leu Thr Asn Ala Pro
115 120 125

Gln Tyr Tyr Val Gly Asp Gln Pro Lys Phe Thr Met Val Val Thr Asn

104

130	135	140
Ile Gly Leu Val Ser Cys Lys Arg Asp Val Gly Ala Ala Val Leu Ala		
145	150	155
Ala Tyr Val Tyr Ser Leu Asp Asn Lys Arg Leu Trp Ser Asn Leu Asp		
165	170	175
Cys Ala Pro Ser Asn Glu Thr Leu Val Lys Thr Phe Ser Pro Gly Glu		
180	185	190
Gln Val Thr Thr Ala Val Thr Trp Thr Gly Met Gly Ser Ala Pro Arg		
195	200	205
Cys Pro Leu Pro Arg Pro Ala Ile Gly Pro Gly Thr Tyr Asn Leu Val		
210	215	220
Val Gln Leu Gly Asn Leu Arg Ser Leu Pro Val Pro Phe Ile Leu Asn		
225	230	235
Gln Pro Pro Pro Pro Gly Pro Val Pro Ala Pro Gly Pro Ala Gln		
245	250	255
Ala Pro Pro Pro Glu Ser Pro Ala Gln Gly Gly		
260	265	

(2) INFORMATION FOR SEQ ID NO:72:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 97 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly Val Gln Val		
1	5	10
Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu Val Val Ala		
20	25	30

105

Gly Gly Ala Ala Ala Asn Ala Gly Val Pro Lys Gly Val Val Val Thr
35 40 45

Lys Val Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu Val Ala Ala
50 55 60

Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr Phe Gln Asp
65 70 75 80

Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly Lys Ala Glu
85 90 95

Gln

(2) INFORMATION FOR SEQ ID NO:73:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 364 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Gly Ala Ala Val Ser Leu Leu Ala Ala Gly Thr Leu Val Leu Thr Ala
1 5 10 15

Cys Gly Gly Gly Thr Asn Ser Ser Ser Ser Gly Ala Gly Gly Thr Ser
20 25 30

Gly Ser Val His Cys Gly Gly Lys Lys Glu Leu His Ser Ser Gly Ser
35 40 45

Thr Ala Gln Glu Asn Ala Met Glu Gln Phe Val Tyr Ala Tyr Val Arg
50 55 60

Ser Cys Pro Gly Tyr Thr Leu Asp Tyr Asn Ala Asn Gly Ser Gly Ala
65 70 75 80

106

Gly Val Thr Gln Phe Leu Asn Asn Glu Thr Asp Phe Ala Gly Ser Asp
85 90 95

Val Pro Leu Asn Pro Ser Thr Gly Gln Pro Asp Arg Ser Ala Glu Arg
100 105 110

Cys Gly Ser Pro Ala Trp Asp Leu Pro Thr Val Phe Gly Pro Ile Ala
115 120 125

Ile Thr Tyr Asn Ile Lys Gly Val Ser Thr Leu Asn Leu Asp Gly Pro
130 135 140

Thr Thr Ala Lys Ile Phe Asn Gly Thr Ile Thr Val Trp Asn Asp Pro
145 150 155 160

Gln Ile Gln Ala Leu Asn Ser Gly Thr Asp Leu Pro Pro Thr Pro Ile
165 170 175

Ser Val Ile Phe Arg Ser Asp Lys Ser Gly Thr Ser Asp Asn Phe Gln
180 185 190

Lys Tyr Leu Asp Gly Val Ser Asn Gly Ala Trp Gly Lys Gly Ala Ser
195 200 205

Glu Thr Phe Ser Gly Gly Val Gly Val Gly Ala Ser Gly Asn Asn Gly
210 215 220

Thr Ser Ala Leu Leu Gln Thr Thr Asp Gly Ser Ile Thr Tyr Asn Glu
225 230 235 240

Trp Ser Phe Ala Val Gly Lys Gln Leu Asn Met Ala Gln Ile Ile Thr
245 250 255

Ser Ala Gly Pro Asp Pro Val Ala Ile Thr Thr Glu Ser Val Gly Lys
260 265 270

Thr Ile Ala Gly Ala Lys Ile Met Gly Gln Gly Asn Asp Leu Val Leu
275 280 285

Asp Thr Ser Ser Phe Tyr Arg Pro Thr Gln Pro Gly Ser Tyr Pro Ile
290 295 300

Val Leu Ala Thr Tyr Glu Ile Val Cys Ser Lys Tyr Pro Asp Ala Thr
305 310 315 320

107

Thr Gly Thr Ala Val Arg Ala Phe Met Gln Ala Ala Ile Gly Pro Gly
325 330 335

Gln Glu Gly Leu Asp Gln Tyr Gly Ser Ile Pro Leu Pro Lys Ser Phe
340 345 350

Gln Ala Lys Leu Ala Ala Ala Val Asn Ala Ile Ser
355 360

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 309 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Gln Ala Ala Ala Gly Arg Ala Val Arg Arg Thr Gly His Ala Glu Asp
1 5 10 15

Gln Thr His Gln Asp Arg Leu His His Gly Cys Arg Arg Ala Ala Val
20 25 30

Val Val Arg Gln Asp Arg Ala Ser Val Ser Ala Thr Ser Ala Arg Pro
35 40 45

Pro Arg Arg His Pro Ala Gln Gly His Arg Arg Arg Val Ala Pro Ser
50 55 60

Gly Gly Arg Arg Arg Pro His Pro His His Val Gln Pro Asp Asp Arg
65 70 75 80

Arg Asp Arg Pro Ala Leu Leu Asp Arg Thr Gln Pro Ala Glu His Pro
85 90 95

Asp Pro His Arg Arg Gly Pro Ala Asp Pro Gly Arg Val Arg Gly Arg
100 105 110

Gly Arg Leu Arg Arg Val Asp Asp Gly Arg Leu Gln Pro Asp Arg Asp

108

115	120	125
Ala Asp His Gly Ala Pro Val Arg Gly Arg Gly Pro His Arg Gly Val		
130	135	140
Gln His Arg Gly Gly Pro Val Phe Val Arg Arg Val Pro Gly Val Arg		
145	150	155
160		
Cys Ala His Arg Arg Gly His Arg Arg Val Ala Ala Pro Gly Gln Gly		
165	170	175
Asp Val Leu Arg Ala Gly Leu Arg Val Glu Arg Leu Arg Pro Val Ala		
180	185	190
Ala Val Glu Asn Leu His Arg Gly Ser Gln Arg Ala Asp Gly Arg Val		
195	200	205
Phe Arg Pro Ile Arg Arg Gly Ala Arg Leu Pro Ala Arg Arg Ser Arg		
210	215	220
Ala Gly Pro Gln Gly Arg Leu His Leu Asp Gly Ala Gly Pro Ser Pro		
225	230	235
240		
Leu Pro Ala Arg Ala Gly Gln Gln Pro Ser Ser Ala Gly Gly Arg		
245	250	255
Arg Ala Gly Gly Ala Glu Arg Ala Asp Pro Gly Gln Arg Gly Arg His		
260	265	270
His Gln Gly Gly His Asp Pro Gly Arg Gln Gly Ala Gln Arg Gly Thr		
275	280	285
Ala Gly Val Ala His Ala Ala Gly Pro Arg Arg Ala Ala Val Arg		
290	295	300
Asn Arg Pro Arg Arg		
305		

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 580 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Ser Ala Val Trp Cys Leu Asn Gly Phe Thr Gly Arg His Arg His Gly
1 5 10 15

Arg Cys Arg Val Arg Ala Ser Gly Trp Arg Ser Ser Asn Arg Trp Cys
20 25 30

Ser Thr Thr Ala Asp Cys Cys Ala Ser Lys Thr Pro Thr Gln Ala Ala
35 40 45

Ser Pro Leu Glu Arg Arg Phe Thr Cys Cys Ser Pro Ala Val Gly Cys
50 55 60

Arg Phe Arg Ser Phe Pro Val Arg Arg Leu Ala Leu Gly Ala Arg Thr
65 70 75 80

Ser Arg Thr Leu Gly Val Arg Arg Thr Leu Ser Gln Trp Asn Leu Ser
85 90 95

Pro Arg Ala Gln Pro Ser Cys Ala Val Thr Val Glu Ser His Thr His
100 105 110

Ala Ser Pro Arg Met Ala Lys Leu Ala Arg Val Val Gly Leu Val Gln
115 120 125

Glu Glu Gln Pro Ser Asp Met Thr Asn His Pro Arg Tyr Ser Pro Pro
130 135 140

Pro Gln Gln Pro Gly Thr Pro Gly Tyr Ala Gln Gly Gln Gln Gln Thr
145 150 155 160

Tyr Ser Gln Gln Phe Asp Trp Arg Tyr Pro Pro Ser Pro Pro Gln
165 170 175

Pro Thr Gln Tyr Arg Gln Pro Tyr Glu Ala Leu Gly Gly Thr Arg Pro
180 185 190

Gly Leu Ile Pro Gly Val Ile Pro Thr Met Thr Pro Pro Pro Gly Met
195 200 205

110

Val Arg Gln Arg Pro Arg Ala Gly Met Leu Ala Ile Gly Ala Val Thr
210 215 220

Ile Ala Val Val Ser Ala Gly Ile Gly Gly Ala Ala Ala Ser Leu Val
225 230 235 240

Gly Phe Asn Arg Ala Pro Ala Gly Pro Ser Gly Gly Pro Val Ala Ala
245 250 255

Ser Ala Ala Pro Ser Ile Pro Ala Ala Asn Met Pro Pro Gly Ser Val
260 265 270

Glu Gln Val Ala Ala Lys Val Val Pro Ser Val Val Met Leu Glu Thr
275 280 285

Asp Leu Gly Arg Gln Ser Glu Glu Gly Ser Gly Ile Ile Leu Ser Ala
290 295 300

Glu Gly Leu Ile Leu Thr Asn Asn His Val Ile Ala Ala Ala Ala Lys
305 310 315 320

Pro Pro Leu Gly Ser Pro Pro Pro Lys Thr Thr Val Thr Phe Ser Asp
325 330 335

Gly Arg Thr Ala Pro Phe Thr Val Val Gly Ala Asp Pro Thr Ser Asp
340 345 350

Ile Ala Val Val Arg Val Gln Gly Val Ser Gly Leu Thr Pro Ile Ser
355 360 365

Leu Gly Ser Ser Ser Asp Leu Arg Val Gly Gln Pro Val Leu Ala Ile
370 375 380

Gly Ser Pro Leu Gly Leu Glu Gly Thr Val Thr Thr Gly Ile Val Ser
385 390 395 400

Ala Leu Asn Arg Pro Val Ser Thr Thr Gly Glu Ala Gly Asn Gln Asn
405 410 415

Thr Val Leu Asp Ala Ile Gln Thr Asp Ala Ala Ile Asn Pro Gly Asn
420 425 430

Ser Gly Gly Ala Leu Val Asn Met Asn Ala Gln Leu Val Gly Val Asn
435 440 445

111

Ser Ala Ile Ala Thr Leu Gly Ala Asp Ser Ala Asp Ala Gln Ser Gly
450 455 460

Ser Ile Gly Leu Gly Phe Ala Ile Pro Val Asp Gln Ala Lys Arg Ile
465 470 475 480

Ala Asp Glu Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly
485 490 495

Val Gln Val Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu
500 505 510

Val Val Ala Gly Gly Ala Ala Asn Ala Gly Val Pro Lys Gly Val
515 520 525

Val Val Thr Lys Val Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu
530 535 540

Val Ala Ala Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr
545 550 555 560

Phe Gln Asp Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly
565 570 575

Lys Ala Glu Gln
580

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 233 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Met Asn Asp Gly Lys Arg Ala Val Thr Ser Ala Val Leu Val Val Leu
1 5 10 15

112

Gly Ala Cys Leu Ala Leu Trp Leu Ser Gly Cys Ser Ser Pro Lys Pro
 20 25 30

Asp Ala Glu Glu Gln Gly Val Pro Val Ser Pro Thr Ala Ser Asp Pro
 35 40 45

Ala Leu Leu Ala Glu Ile Arg Gln Ser Leu Asp Ala Thr Lys Gly Leu
 50 55 60

Thr Ser Val His Val Ala Val Arg Thr Thr Gly Lys Val Asp Ser Leu
 65 70 75 80

Leu Gly Ile Thr Ser Ala Asp Val Asp Val Arg Ala Asn Pro Leu Ala
 85 90 95

Ala Lys Gly Val Cys Thr Tyr Asn Asp Glu Gln Gly Val Pro Phe Arg
 100 105 110

Val Gln Gly Asp Asn Ile Ser Val Lys Leu Phe Asp Asp Trp Ser Asn
 115 120 125

Leu Gly Ser Ile Ser Glu Leu Ser Thr Ser Arg Val Leu Asp Pro Ala
 130 135 140

Ala Gly Val Thr Gln Leu Leu Ser Gly Val Thr Asn Leu Gln Ala Gln
 145 150 155 160

Gly Thr Glu Val Ile Asp Gly Ile Ser Thr Thr Lys Ile Thr Gly Thr
 165 170 175

Ile Pro Ala Ser Ser Val Lys Met Leu Asp Pro Gly Ala Lys Ser Ala
 180 185 190

Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser His His Leu Val
 195 200 205

Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln Leu Thr Gln Ser
 210 215 220

Lys Trp Asn Glu Pro Val Asn Val Asp
 225 230

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 66 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Val Ile Asp Ile Ile Gly Thr Ser Pro Thr Ser Trp Glu Gln Ala Ala
1 5 10 15

Ala Glu Ala Val Gln Arg Ala Arg Asp Ser Val Asp Asp Ile Arg Val
20 25 30

Ala Arg Val Ile Glu Gln Asp Met Ala Val Asp Ser Ala Gly Lys Ile
35 40 45

Thr Tyr Arg Ile Lys Leu Glu Val Ser Phe Lys Met Arg Pro Ala Gln
50 55 60

Pro Arg
65

(2) INFORMATION FOR SEQ ID NO:78:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 69 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Val Pro Pro Ala Pro Pro Leu Pro Pro Leu Pro Pro Ser Pro Ile Ser
1 5 10 15

Cys Ala Ser Pro Pro Ser Pro Pro Leu Pro Pro Ala Pro Pro Val Ala
20 25 30

Pro Gly Pro Pro Met Pro Pro Leu Asp Pro Trp Pro Pro Ala Pro Pro
35 40 45

Leu Pro Tyr Ser Thr Pro Pro Gly Ala Pro Leu Pro Pro Ser Pro Pro
50 55 60

Ser Pro Pro Leu Pro
65

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 355 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Met Ser Asn Ser Arg Arg Arg Ser Leu Arg Trp Ser Trp Leu Leu Ser
1 5 10 15

Val Leu Ala Ala Val Gly Leu Gly Leu Ala Thr Ala Pro Ala Gln Ala
20 25 30

Ala Pro Pro Ala Leu Ser Gln Asp Arg Phe Ala Asp Phe Pro Ala Leu
35 40 45

Pro Leu Asp Pro Ser Ala Met Val Ala Gln Val Ala Pro Gln Val Val
50 55 60

Asn Ile Asn Thr Lys Leu Gly Tyr Asn Asn Ala Val Gly Ala Gly Thr
65 70 75 80

Gly Ile Val Ile Asp Pro Asn Gly Val Val Leu Thr Asn Asn His Val
85 90 95

Ile Ala Gly Ala Thr Asp Ile Asn Ala Phe Ser Val Gly Ser Gly Gln
100 105 110

115

Thr Tyr Gly Val Asp Val Val Gly Tyr Asp Arg Thr Gln Asp Val Ala
115 120 125

Val Leu Gln Leu Arg Gly Ala Gly Gly Leu Pro Ser Ala Ala Ile Gly
130 135 140

Gly Gly Val Ala Val Gly Glu Pro Val Val Ala Met Gly Asn Ser Gly
145 150 155 160

Gly Gln Gly Gly Thr Pro Arg Ala Val Pro Gly Arg Val Val Ala Leu
165 170 175

Gly Gln Thr Val Gln Ala Ser Asp Ser Leu Thr Gly Ala Glu Glu Thr
180 185 190

Leu Asn Gly Leu Ile Gln Phe Asp Ala Ala Ile Gln Pro Gly Asp Ser
195 200 205

Gly Gly Pro Val Val Asn Gly Leu Gly Gln Val Val Gly Met Asn Thr
210 215 220

Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gln Gly Phe Ala
225 230 235 240

Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser Gly
245 250 255

Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly Leu
260 265 270

Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val Val
275 280 285

Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val Ile
290 295 300

Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala Asp
305 310 315 320

Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp Gln
325 330 335

Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu Gly
340 345 350

Pro Pro Ala
355

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 205 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Ser Pro Lys Pro Asp Ala Glu Glu Gln Gly Val Pro Val Ser Pro Thr
1 5 10 15

Ala Ser Asp Pro Ala Leu Leu Ala Glu Ile Arg Gln Ser Leu Asp Ala
20 25 30

Thr Lys Gly Leu Thr Ser Val His Val Ala Val Arg Thr Thr Gly Lys
35 40 45

Val Asp Ser Leu Leu Gly Ile Thr Ser Ala Asp Val Asp Val Arg Ala
50 55 60

Asn Pro Leu Ala Ala Lys Gly Val Cys Thr Tyr Asn Asp Glu Gln Gly
65 70 75 80

Val Pro Phe Arg Val Gln Gly Asp Asn Ile Ser Val Lys Leu Phe Asp
85 90 95

Asp Trp Ser Asn Leu Gly Ser Ile Ser Glu Leu Ser Thr Ser Arg Val
100 105 110

Leu Asp Pro Ala Ala Gly Val Thr Gln Leu Leu Ser Gly Val Thr Asn
115 120 125

Leu Gln Ala Gln Gly Thr Glu Val Ile Asp Gly Ile Ser Thr Thr Lys
130 135 140

Ile Thr Gly Thr Ile Pro Ala Ser Ser Val Lys Met Leu Asp Pro Gly

145	150	155	160
Ala Lys Ser Ala Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser			
165		170	175
His His Leu Val Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln			
180		185	190
Leu Thr Gln Ser Lys Trp Asn Glu Pro Val Asn Val Asp			
195		200	205

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 286 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

Gly	Asp	Ser	Phe	Trp	Ala	Ala	Asp	Gln	Met	Ala	Arg	Gly	Phe	Val
1				5			10			15				
Leu Gly Ala Thr Ala Gly Arg Thr Thr Leu Thr Gly Glu Gly Leu Gln														
				20			25			30				
His Ala Asp Gly His Ser Leu Leu Leu Asp Ala Thr Asn Pro Ala Val														
				35			40			45				
Val Ala Tyr Asp Pro Ala Phe Ala Tyr Glu Ile Gly Tyr Ile Xaa Glu														
				50			55			60				
Ser Gly Leu Ala Arg Met Cys Gly Glu Asn Pro Glu Asn Ile Phe Phe														
				65			70			75			80	
Tyr Ile Thr Val Tyr Asn Glu Pro Tyr Val Gln Pro Pro Glu Pro Glu														
				85			90			95				
Asn Phe Asp Pro Glu Gly Val Leu Gly Gly Ile Tyr Arg Tyr His Ala														
				100			105			110				

Ala Thr Glu Gln Arg Thr Asn Lys Xaa Gln Ile Leu Ala Ser Gly Val
115 120 125

Ala Met Pro Ala Ala Leu Arg Ala Ala Gln Met Leu Ala Ala Glu Trp
130 135 140

Asp Val Ala Ala Asp Val Trp Ser Val Thr Ser Trp Gly Glu Leu Asn
145 150 155 160

Arg Asp Gly Val Val Ile Glu Thr Glu Lys Leu Arg His Pro Asp Arg
165 170 175

Pro Ala Gly Val Pro Tyr Val Thr Arg Ala Leu Glu Asn Ala Arg Gly
180 185 190

Pro Val Ile Ala Val Ser Asp Trp Met Arg Ala Val Pro Glu Gln Ile
195 200 205

Arg Pro Trp Val Pro Gly Thr Tyr Leu Thr Leu Gly Thr Asp Gly Phe
210 215 220

Gly Phe Ser Asp Thr Arg Pro Ala Gly Arg Arg Tyr Phe Asn Thr Asp
225 230 235 240

Ala Glu Ser Gln Val Gly Arg Gly Phe Gly Arg Gly Trp Pro Gly Arg
245 250 255

Arg Val Asn Ile Asp Pro Phe Gly Ala Gly Arg Gly Pro Pro Ala Gln
260 265 270

Leu Pro Gly Phe Asp Glu Gly Gly Leu Arg Pro Xaa Lys
275 280 285

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 173 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Thr Lys Phe His Ala Leu Met Gln Glu Gln Ile His Asn Glu Phe Thr
1 5 10 15

Ala Ala Gln Gln Tyr Val Ala Ile Ala Val Tyr Phe Asp Ser Glu Asp
20 25 30

Leu Pro Gln Leu Ala Lys His Phe Tyr Ser Gln Ala Val Glu Glu Arg
35 40 45

Asn His Ala Met Met Leu Val Gln His Leu Leu Asp Arg Asp Leu Arg
50 55 60

Val Glu Ile Pro Gly Val Asp Thr Val Arg Asn Gln Phe Asp Arg Pro
65 70 75 80

Arg Glu Ala Leu Ala Leu Asp Gln Glu Arg Thr Val Thr Asp
85 90 95

Gln Val Gly Arg Leu Thr Ala Val Ala Arg Asp Glu Gly Asp Phe Leu
100 105 110

Gly Glu Gln Phe Met Gln Trp Phe Leu Gln Glu Gln Ile Glu Glu Val
115 120 125

Ala Leu Met Ala Thr Leu Val Arg Val Ala Asp Arg Ala Gly Ala Asn
130 135 140

Leu Phe Glu Leu Glu Asn Phe Val Ala Arg Glu Val Asp Val Ala Pro
145 150 155 160

Ala Ala Ser Gly Ala Pro His Ala Ala Gly Gly Arg Leu
165 170

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 107 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

120

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Arg Ala Asp Glu Arg Lys Asn Thr Thr Met Lys Met Val Lys Ser Ile
1 5 10 15

Ala Ala Gly Leu Thr Ala Ala Ala Ala Ile Gly Ala Ala Ala Ala Gly
20 25 30

Val Thr Ser Ile Met Ala Gly Gly Pro Val Val Tyr Gln Met Gln Pro
35 40 45

Val Val Phe Gly Ala Pro Leu Pro Leu Asp Pro Xaa Ser Ala Pro Xaa
50 55 60

Val Pro Thr Ala Ala Gln Trp Thr Xaa Leu Leu Asn Xaa Leu Xaa Asp
65 70 75 80

Pro Asn Val Ser Phe Xaa Asn Lys Gly Ser Leu Val Glu Gly Gly Ile
85 90 95

Gly Gly Xaa Glu Gly Xaa Xaa Arg Arg Xaa Gln
100 105

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 125 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Val Leu Ser Val Pro Val Gly Asp Gly Phe Trp Xaa Arg Val Val Asn
1 5 10 15

Pro Leu Gly Gln Pro Ile Asp Gly Arg Gly Asp Val Asp Ser Asp Thr
20 25 30

121

Arg	Arg	Ala	Leu	Glu	Leu	Gln	Ala	Pro	Ser	Val	Val	Xaa	Arg	Gln	Gly
35							40						45		
Val	Lys	Glu	Pro	Leu	Xaa	Thr	Gly	Ile	Lys	Ala	Ile	Asp	Ala	Met	Thr
50							55					60			
Pro	Ile	Gly	Arg	Gly	Gln	Arg	Gln	Leu	Ile	Ile	Gly	Asp	Arg	Lys	Thr
65							70					75			80
Gly	Lys	Asn	Arg	Arg	Leu	Cys	Arg	Thr	Pro	Ser	Ser	Asn	Gln	Arg	Glu
85												90			95
Glu	Leu	Gly	Val	Arg	Trp	Ile	Pro	Arg	Ser	Arg	Cys	Ala	Cys	Val	Tyr
100								105					110		
Val	Gly	His	Arg	Ala	Arg	Arg	Gly	Thr	Tyr	His	Arg	Arg			
115							120					125			

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 117 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Cys	Asp	Ala	Val	Met	Gly	Phe	Leu	Gly	Gly	Ala	Gly	Pro	Leu	Ala	Val
1				5						10					15
Val	Asp	Gln	Gln	Leu	Val	Thr	Arg	Val	Pro	Gln	Gly	Trp	Ser	Phe	Ala
20				25									30		
Gln	Ala	Ala	Ala	Val	Pro	Val	Val	Phe	Leu	Thr	Ala	Trp	Tyr	Gly	Leu
35								40				45			
Ala	Asp	Leu	Ala	Glu	Ile	Lys	Ala	Gly	Glu	Ser	Val	Leu	Ile	His	Ala
50							55					60			
Gly	Thr	Gly	Gly	Val	Gly	Met	Ala	Ala	Val	Gln	Leu	Ala	Arg	Gln	Trp

122

65

70

75

80

Gly Val Glu Val Phe Val Thr Ala Ser Arg Gly Lys Trp Asp Thr Leu
85 90 95

Arg Ala Xaa Xaa Phe Asp Asp Xaa Pro Tyr Arg Xaa Phe Pro His Xaa
100 105 110

Arg Ser Ser Xaa Gly
115

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 103 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Met Tyr Arg Phe Ala Cys Arg Thr Leu Met Leu Ala Ala Cys Ile Leu
1 5 10 15

Ala Thr Gly Val Ala Gly Leu Gly Val Gly Ala Gln Ser Ala Ala Gln
20 25 30

Thr Ala Pro Val Pro Asp Tyr Tyr Trp Cys Pro Gly Gln Pro Phe Asp
35 40 45

Pro Ala Trp Gly Pro Asn Trp Asp Pro Tyr Thr Cys His Asp Asp Phe
50 55 60

His Arg Asp Ser Asp Gly Pro Asp His Ser Arg Asp Tyr Pro Gly Pro
65 70 75 80

Ile Leu Glu Gly Pro Val Leu Asp Asp Pro Gly Ala Ala Pro Pro Pro
85 90 95

Pro Ala Ala Gly Gly Gly Ala
100

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 88 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Val Gln Cys Arg Val Trp Leu Glu Ile Gln Trp Arg Gly Met Leu Gly
1 5 10 15

Ala Asp Gln Ala Arg Ala Gly Gly Pro Ala Arg Ile Trp Arg Glu His
20 25 30

Ser Met Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala
35 40 45

Thr Lys Glu Gly Arg Gly Ile Val Met Arg Val Pro Leu Glu Gly Gly
50 55 60

Gly Arg Leu Val Val Glu Leu Thr Pro Asp Glu Ala Ala Leu Gly
65 70 75 80

Asp Glu Leu Lys Gly Val Thr Ser
85

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 95 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Thr Asp Ala Ala Thr Leu Ala Gln Glu Ala Gly Asn Phe Glu Arg Ile
1 5 10 15

Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala Gly
20 25 30

Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln Ala
35 40 45

Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu Leu
50 55 60

Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg
65 70 75 80

Ala Asp Glu Glu Gln Gln Ala Leu Ser Ser Gln Met Gly Phe
85 90 95

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 166 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Met Thr Gln Ser Gln Thr Val Thr Val Asp Gln Gln Glu Ile Leu Asn
1 5 10 15

Arg Ala Asn Glu Val Glu Ala Pro Met Ala Asp Pro Pro Thr Asp Val
20 25 30

Pro Ile Thr Pro Cys Glu Leu Thr Xaa Xaa Lys Asn Ala Ala Gln Gln
35 40 45

Xaa Val Leu Ser Ala Asp Asn Met Arg Glu Tyr Leu Ala Ala Gly Ala
50 55 60

125

Lys Glu Arg Gln Arg Leu Ala Thr Ser Leu Arg Asn Ala Ala Lys Xaa
65 70 75 80

Tyr Gly Glu Val Asp Glu Glu Ala Ala Thr Ala Leu Asp Asn Asp Gly
85 90 95

Glu Gly Thr Val Gln Ala Glu Ser Ala Gly Ala Val Gly Gly Asp Ser
100 105 110

Ser Ala Glu Leu Thr Asp Thr Pro Arg Val Ala Thr Ala Gly Glu Pro
115 120 125

Asn Phe Met Asp Leu Lys Glu Ala Ala Arg Lys Leu Glu Thr Gly Asp
130 135 140

Gln Gly Ala Ser Leu Ala His Xaa Gly Asp Gly Trp Asn Thr Xaa Thr
145 150 155 160

Leu Thr Leu Gln Gly Asp
165

(2) INFORMATION FOR SEQ ID NO:90:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 5 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Arg Ala Glu Arg Met
1 5

(2) INFORMATION FOR SEQ ID NO:91:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 263 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single

(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Val Ala Trp Met Ser Val Thr Ala Gly Gln Ala Glu Leu Thr Ala Ala
1 5 10 15

Gln Val Arg Val Ala Ala Ala Tyr Glu Thr Ala Tyr Gly Leu Thr
20 25 30

Val Pro Pro Pro Val Ile Ala Glu Asn Arg Ala Glu Leu Met Ile Leu
35 40 45

Ile Ala Thr Asn Leu Leu Gly Gln Asn Thr Pro Ala Ile Ala Val Asn
50 55 60

Glu Ala Glu Tyr Gly Glu Met Trp Ala Gln Asp Ala Ala Ala Met Phe
65 70 75 80

Gly Tyr Ala Ala Ala Thr Ala Thr Ala Thr Leu Leu Pro Phe
85 90 95

Glu Glu Ala Pro Glu Met Thr Ser Ala Gly Gly Leu Leu Glu Gln Ala
100 105 110

Ala Ala Val Glu Glu Ala Ser Asp Thr Ala Ala Ala Asn Gln Leu Met
115 120 125

Asn Asn Val Pro Gln Ala Leu Lys Gln Leu Ala Gln Pro Thr Gln Gly
130 135 140

Thr Thr Pro Ser Ser Lys Leu Gly Gly Leu Trp Lys Thr Val Ser Pro
145 150 155 160

His Arg Ser Pro Ile Ser Asn Met Val Ser Met Ala Asn Asn His Met
165 170 175

Ser Met Thr Asn Ser Gly Val Ser Met Thr Asn Thr Leu Ser Ser Met
180 185 190

Leu Lys Gly Phe Ala Pro Ala Ala Ala Gln Ala Val Gln Thr Ala

127

195

200

205

Ala Gln Asn Gly Val Arg Ala Met Ser Ser Leu Gly Ser Ser Leu Gly
210 215 220

Ser Ser Gly Leu Gly Gly Val Ala Ala Asn Leu Gly Arg Ala Ala
225 230 235 240

Ser Val Arg Tyr Gly His Arg Asp Gly Gly Lys Tyr Ala Xaa Ser Gly
245 250 255

Arg Arg Asn Gly Gly Pro Ala
260

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 303 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Met Thr Tyr Ser Pro Gly Asn Pro Gly Tyr Pro Gln Ala Gln Pro Ala
1 5 10 15

Gly Ser Tyr Gly Gly Val Thr Pro Ser Phe Ala His Ala Asp Glu Gly
20 25 30

Ala Ser Lys Leu Pro Met Tyr Leu Asn Ile Ala Val Ala Val Leu Gly
35 40 45

Leu Ala Ala Tyr Phe Ala Ser Phe Gly Pro Met Phe Thr Leu Ser Thr
50 55 60

Glu Leu Gly Gly Asp Gly Ala Val Ser Gly Asp Thr Gly Leu Pro
65 70 75 80

Val Gly Val Ala Leu Leu Ala Ala Leu Leu Ala Gly Val Val Leu Val
85 90 95

Pro Lys Ala Lys Ser His Val Thr Val Val Ala Val Leu Gly Val Leu
100 105 110

Gly Val Phe Leu Met Val Ser Ala Thr Phe Asn Lys Pro Ser Ala Tyr
115 120 125

Ser Thr Gly Trp Ala Leu Trp Val Val Leu Ala Phe Ile Val Phe Gln
130 135 140

Ala Val Ala Ala Val Leu Ala Leu Leu Val Glu Thr Gly Ala Ile Thr
145 150 155 160

Ala Pro Ala Pro Arg Pro Lys Phe Asp Pro Tyr Gly Gln Tyr Gly Arg
165 170 175

Tyr Gly Gln Tyr Gly Gln Tyr Gly Val Gln Pro Gly Gly Tyr Tyr Gly
180 185 190

Gln Gln Gly Ala Gln Gln Ala Ala Gly Leu Gln Ser Pro Gly Pro Gln
195 200 205

Gln Ser Pro Gln Pro Pro Gly Tyr Gly Ser Gln Tyr Gly Gly Tyr Ser
210 215 220

Ser Ser Pro Ser Gln Ser Gly Ser Gly Tyr Thr Ala Gln Pro Pro Ala
225 230 235 240

Gln Pro Pro Ala Gln Ser Gly Ser Gln Gln Ser His Gln Gly Pro Ser
245 250 255

Thr Pro Pro Thr Gly Phe Pro Ser Phe Ser Pro Pro Pro Pro Val Ser
260 265 270

Ala Gly Thr Gly Ser Gln Ala Gly Ser Ala Pro Val Asn Tyr Ser Asn
275 280 285

Pro Ser Gly Gly Glu Gln Ser Ser Ser Pro Gly Gly Ala Pro Val
290 295 300

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 amino acids
- (B) TYPE: amino acid

129

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Gly	Cys	Gly	Glu	Thr	Asp	Ala	Ala	Thr	Leu	Ala	Gln	Glu	Ala	Gly	Asn
1				5					10					15	
Phe	Glu	Arg	Ile	Ser	Gly	Asp	Leu	Lys	Thr	Gln	Ile				
				20				25							

(2) INFORMATION FOR SEQ ID NO:94:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Asp	Gln	Val	Glu	Ser	Thr	Ala	Gly	Ser	Leu	Gln	Gly	Gln	Trp	Arg	Gly
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO:95:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

130

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Gly	Cys	Gly	Ser	Thr	Ala	Gly	Ser	Leu	Gln	Gly	Gln	Trp	Arg	Gly	Ala
1				5					10				15		
Ala	Gly	Thr	Ala	Ala	Gln	Ala	Ala	Val	Val	Val	Arg				
				20				25							

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Gly	Cys	Gly	Gly	Thr	Ala	Ala	Gln	Ala	Ala	Val	Val	Arg	Phe	Gln	Glu
1				5					10				15		
Ala	Ala	Asn	Lys	Gln	Lys	Gln	Glu	Leu	Asp	Glu					
				20				25							

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

Gly	Cys	Gly	Ala	Asn	Lys	Gln	Lys	Gln	Glu	Leu	Asp	Glu	Ile	Ser	Thr
1				5					10				15		

Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg
 20 25

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Gly Cys Gly Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg Ala Asp Glu
 1 5 10 15

Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe
 20 25

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 507 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

ATGAAGATGG TGAAATCGAT CGCCGCAGGT CTGACCGCCG CGGCTGCAAT CGGCGCCGCT	60
GC GGCCGGTG TGACTTCGAT CATGGCTGGC GGCCCGGTG TATAACCAGAT GCAGCCGGTC	120
GTCTTCGGCG CGCCACTGCC GTTGGACCCG GCATCCGCC CTGACGTCCC GACCGCCGCC	180
CAGTTGACCA GCCTGCTCAA CAGCCTGCC GATCCCAACG TGTCGTTGC GAACAAGGGC	240

AGTCTGGTCG AGGGCGGCAT CGGGGGCACC GAGGCGCGCA TCGCCGACCA CAAGCTGAAG	300
AAGGCCGCCG AGCACGGGGA TCTGCCGCTG TCGTTCAGCG TGACGAACAT CCAGCCGGCG	360
GCCGCCGGTT CGGCCACCGC CGACGTTTCC GTCTCGGGTC CGAAGCTCTC GTCGCCGGTC	420
ACGCAGAACG TCACGTTCGT GAATCAAGGC GGCTGGATGC TGTCACGCGC ATCGGCGATG	480
GAGTTGCTGC AGGCCGCAGG GAACTGA	507

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 168 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

Met Lys Met Val Lys Ser Ile Ala Ala Gly Leu Thr Ala Ala Ala Ala			
1	5	10	15
Ile Gly Ala Ala Ala Ala Gly Val Thr Ser Ile Met Ala Gly Gly Pro			
20	25	30	
Val Val Tyr Gln Met Gln Pro Val Val Phe Gly Ala Pro Leu Pro Leu			
35	40	45	
Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln Leu Thr Ser			
50	55	60	
Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala Asn Lys Gly			
65	70	75	80
Ser Leu Val Glu Gly Gly Ile Gly Gly Thr Glu Ala Arg Ile Ala Asp			
85	90	95	
His Lys Leu Lys Lys Ala Ala Glu His Gly Asp Leu Pro Leu Ser Phe			
100	105	110	

133

Ser Val Thr Asn Ile Gln Pro Ala Ala Ala Gly Ser Ala Thr Ala Asp
 115 120 125
 Val Ser Val Ser Gly Pro Lys Leu Ser Ser Pro Val Thr Gln Asn Val
 130 135 140
 Thr Phe Val Asn Gln Gly Gly Trp Met Leu Ser Arg Ala Ser Ala Met
 145 150 155 160
 Glu Leu Leu Gln Ala Ala Gly Asn
 165

(2) INFORMATION FOR SEQ ID NO:101:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 500 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

CGTGGCAATG TCGTTGACCG TCGGGGCCGG GGTGCCTCC GCAGATCCCG TGGACGCGGT	60
CATTAACACC ACCTGCAATT ACGGGCAGGT AGTAGCTGCG CTCAACGCGA CGGATCCGGG	120
GGCTGCCGCA CAGTTAACCG CCTCACCGGT GGCGCAGTCC TATTTGCGCA ATTCCTCGC	180
CGCACCGCCA CCTCAGCGCG CTGCCATGGC CGCGCAATTG CAAGCTGTGC CGGGGGCGGC	240
ACAGTACATC GGCTTGTCG AGTCGGTTGC CGGCTCCTGC AACAACTATT AAGCCCATGC	300
GGGCCCCATC CCGCGACCCG GCATCGTCGC CGGGGCTAGG CCAGATTGCC CCGCTCCTCA	360
ACGGGCCGCA TCCCGCGACC CGGCATCGTC GCCGGGGCTA GGCCAGATTG CCCCCTCCT	420
CAACGGGCCG CATCTCGTGC CGAATTCTG CAGCCCCGGG GATCCACTAG TTCTAGAGCG	480
GCCGCCACCG CGGTGGAGCT	500

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 96 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

Val Ala Met Ser Leu Thr Val Gly Ala Gly Val Ala Ser Ala Asp Pro
1 5 10 15

Val Asp Ala Val Ile Asn Thr Thr Cys Asn Tyr Gly Gln Val Val Ala
20 25 30

Ala Leu Asn Ala Thr Asp Pro Gly Ala Ala Ala Gln Phe Asn Ala Ser
35 40 45

Pro Val Ala Gln Ser Tyr Leu Arg Asn Phe Leu Ala Ala Pro Pro Pro
50 55 60

Gln Arg Ala Ala Met Ala Ala Gln Leu Gln Ala Val Pro Gly Ala Ala
65 70 75 80

Gln Tyr Ile Gly Leu Val Glu Ser Val Ala Gly Ser Cys Asn Asn Tyr
85 90 95

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 154 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

ATGACAGAGC AGCAGTGGAA TTTCGCGGGT ATCGAGGCCG CGGCAAGCGC AATCCAGGGA	60
AATGTCACGT CCATTCAATT CCTCCTTGAC GAGGGGAAGC AGTCCCTGAC CAAGCTCGCA	120
GC GG C CTGGG GCGGTAGCGG TTCGGAAGCG TACC	154

(2) INFORMATION FOR SEQ ID NO:104:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 51 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Met Thr Glu Gln Gln Trp Asn Phe Ala Gly Ile Glu Ala Ala Ala Ser			
1	5	10	15
Ala Ile Gln Gly Asn Val Thr Ser Ile His Ser Leu Leu Asp Glu Gly			
20	25	30	
Lys Gln Ser Leu Thr Lys Leu Ala Ala Ala Trp Gly Gly Ser Gly Ser			
35	40	45	
Glu Ala Tyr			
50			

(2) INFORMATION FOR SEQ ID NO:105:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 282 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

CGGTCGCGCA CTTCCAGGTG ACTATGAAAG TCGGCTTCCG NCTGGAGGAT TCCTGAACCT	60
TCAAGCGCGG CCGATAACTG AGGTGCATCA TTAAGCGACT TTTCCAGAAC ATCCTGACGC	120
GCTCGAAACG CGGCACAGCC GACGGTGGCT CCGNCGAGGC GCTGNCTCCA AAATCCCTGA	180
GACAATTCGN CGGGGGCGCC TACAAGGAAG TCGGTGCTGA ATTGNCGNG TATCTGGTCG	240
ACCTGTGTGG TCTGNAGCCG GACGAAGCGG TGCTCGACGT CG	282

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1565 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

GTATGCGGCC ACTGAAGTCG CCAATGCGGC GGCGGCCAGC TAAGCCAGGA ACAGTCGGCA	60
CGAGAAACCA CGAGAAATAG GGACACGTAA TGGTGGATTT CGGGGCGTTA CCACCGGAGA	120
TCAACTCCGC GAGGATGTAC GCCGGCCCGG GTTGGCCTC GCTGGTGGCC GCGGCTCAGA	180
TGTGGGACAG CGTGGCGAGT GACCTGTTTT CGGCCGCGTC GGCGTTTCAG TCGGTGGTCT	240
GGGGTCTGAC GGTGGGGTCG TGGATAGGTT CGTCGGCGGG TCTGATGGTG GCGGCGGCCT	300
CGCCGTATGT GGCGTGGATG AGCGTCACCG CGGGGCAGGC CGAGCTGACC GCCGCCAGG	360
TCCGGGTTGC TGCAGCGGCC TACGAGACGG CGTATGGGCT GACGGTGGCC CCGCCGGTGA	420
TCGCCGAGAA CCGTGCTGAA CTGATGATTC TGATAGCGAC CAACCTTTG GGGCAAAACA	480
CCCCGGCGAT CGCGGTCAAC GAGGCCGAAT ACGGCGAGAT GTGGGCCAA GACGCCGCCG	540
CGATGTTGG CTACGCCGCG GCGACGGCGA CGGCACGGC GACGTTGCTG CCGTTCGAGG	600

AGGCGCCGGA GATGACCAGC GC GG GTGGGC TCCTCGAGCA GGCCGCCGCG GTCGAGGAGG	660
CCTCCGACAC CGCCGCGGCG AAC CAGTTGA TGAACAATGT GCCCCAGGCG CTGCAACAGC	720
TGGCCCAGCC CACGCAGGGC ACCACGCC TT CTTCCAAGCT GGGTGGCCTG TGGAAGACGG	780
TCTCGCCGCA TCGGTGCGCG ATCAGCAACA TGGTGTCAAT GGCCAACAAC CACATGTCAA	840
TGACCAACTC GGGTGTGTCA ATGACCAACA CCTTGAGCTC GATGTTGAAG GGCTTGCTC	900
CGGCGGGCGGC CGCCCAGGCC GTGCAAACCG CGCGCAAAA CGGGGTCCGG GCGATGAGCT	960
CGCTGGGCAG CTCGCTGGGT TCTTCGGGTC TGGGCGGTGG GGTGGCCGCC AACTTGGGTC	1020
GGGCGGCCTC GGTCGGTTCG TTGTCGGTGC CGCAGGCCTG GGCGCGGCC AAC CAGGCAG	1080
TCACCCCCGGC GGC GCGGGCG CTGCCGCTGA CCAGCCTGAC CAGCGCCGCG GAAAGAGGGC	1140
CGGGGCAGAT GCTGGGCAGGG CTGCCGGTGG GGCAGATGGG CGCCAGGGCC GGTGGTGGC	1200
TCAGTGGTGT GCTGCGTGT CCTCGCGAC CCTATGTGAT GCCGCATTCT CGGGCGGCCG	1260
GCTAGGAGAG GGGCGCAGA CTGTCGTTAT TTGACCAAGTG ATCGGCGGTC TCGGTGTTTC	1320
CGCGGCCGGC TATGACAACA GTCAATGTGC ATGACAAGTT ACAGGTATTA GGTCCAGGTT	1380
CAACAAGGAG ACAGGCAACA TGGCCTCACG TTTTATGACG GATCCGCACG CGATGCGGGA	1440
CATGGCGGGC CGTTTGAAAG TGCACGCCA GACGGTGGAG GACGAGGCTC GCCGGATGTG	1500
GGCGTCCGCG CAAAACATT CCGGTGCGGG CTGGAGTGGC ATGGCCGAGG CGACCTCGCT	1560
AGACA	1565

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 391 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

Met Val Asp Phe Gly Ala Leu Pro Pro Glu Ile Asn Ser Ala Arg Met
1 5 10 15

Tyr Ala Gly Pro Gly Ser Ala Ser Leu Val Ala Ala Ala Gln Met Trp
20 25 30

Asp Ser Val Ala Ser Asp Leu Phe Ser Ala Ala Ser Ala Phe Gln Ser
35 40 45

Val Val Trp Gly Leu Thr Val Gly Ser Trp Ile Gly Ser Ser Ala Gly
50 55 60

Leu Met Val Ala Ala Ala Ser Pro Tyr Val Ala Trp Met Ser Val Thr
65 70 75 80

Ala Gly Gln Ala Glu Leu Thr Ala Ala Gln Val Arg Val Ala Ala Ala
85 90 95

Ala Tyr Glu Thr Ala Tyr Gly Leu Thr Val Pro Pro Pro Val Ile Ala
100 105 110

Glu Asn Arg Ala Glu Leu Met Ile Leu Ile Ala Thr Asn Leu Leu Gly
115 120 125

Gln Asn Thr Pro Ala Ile Ala Val Asn Glu Ala Glu Tyr Gly Glu Met
130 135 140

Trp Ala Gln Asp Ala Ala Ala Met Phe Gly Tyr Ala Ala Ala Thr Ala
145 150 155 160

Thr Ala Thr Ala Thr Leu Leu Pro Phe Glu Glu Ala Pro Glu Met Thr
165 170 175

Ser Ala Gly Gly Leu Leu Glu Gln Ala Ala Ala Val Glu Glu Ala Ser
180 185 190

Asp Thr Ala Ala Ala Asn Gln Leu Met Asn Asn Val Pro Gln Ala Leu
195 200 205

Gln Gln Leu Ala Gln Pro Thr Gln Gly Thr Thr Pro Ser Ser Lys Leu
210 215 220

Gly Gly Leu Trp Lys Thr Val Ser Pro His Arg Ser Pro Ile Ser Asn
225 230 235 240

Met Val Ser Met Ala Asn Asn His Met Ser Met Thr Asn Ser Gly Val
245 250 255

Ser Met Thr Asn Thr Leu Ser Ser Met Leu Lys Gly Phe Ala Pro Ala
260 265 270

Ala Ala Ala Gln Ala Val Gln Thr Ala Ala Gln Asn Gly Val Arg Ala
275 280 285

Met Ser Ser Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Gly Gly
290 295 300

Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser Val
305 310 315 320

Pro Gln Ala Trp Ala Ala Asn Gln Ala Val Thr Pro Ala Ala Arg
325 330 335

Ala Leu Pro Leu Thr Ser Leu Thr Ser Ala Ala Glu Arg Gly Pro Gly
340 345 350

Gln Met Leu Gly Gly Leu Pro Val Gly Gln Met Gly Ala Arg Ala Gly
355 360 365

Gly Gly Leu Ser Gly Val Leu Arg Val Pro Pro Arg Pro Tyr Val Met
370 375 380

Pro His Ser Pro Ala Ala Gly
385 390

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 259 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

ACCAACACCT TGCACTCNAT GTTGAAGGGC TTAGCTCCGG CGGC GGCTCA GGCGTGAA	60
ACCGCGGCGG AAAACGGGGT CTGGGCAATG AGCTCGCTGG GCAGCCAGCT GGGTTCGTCC	120
CTGGGTTCTT CGGGTCTGGG CGCTGGGTG GCCGCCAACT TGGGTCGGGC GGCCCTCGGTC	180
GGTTCGTTGT CGGTGCCGCC AGCATGGGCC GCGGCCAACC AGGCGGTAC CCCGGCGGCG	240
CGGGCGCTGC CGCTGACCA	259

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 86 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Thr Asn Thr Leu His Ser Met Leu Lys Gly Leu Ala Pro Ala Ala Ala			
1	5	10	15
Gln Ala Val Glu Thr Ala Ala Glu Asn Gly Val Trp Ala Met Ser Ser			
20	25	30	
Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Ala			
35	40	45	
Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser			
50	55	60	
Val Pro Pro Ala Trp Ala Ala Asn Gln Ala Val Thr Pro Ala Ala			
65	70	75	80
Arg Ala Leu Pro Leu Thr			
85			

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1109 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

TACTTGAGAG AATTTGACCT GTGCCGACG TTGTTTGTG TCCATCATG GTGCTAGTTA	60
TGGCCGAGCG GAAGGATTAT CGAAAGTGGTG GACTTCGGGG CGTTACCACC GGAGATCAAC	120
TCCCGCGAGGA TGTACGCCGG CCCGGGTTCG GCCTCGCTGG TGGCCGCCGC GAAGATGTGG	180
GACAGCGTGG CGAGTGACCT GTTTTGGCC GCGTCGGCGT TTCAGTCGGT GGTCTGGGGT	240
CTGACGACGG GATCGTGGAT AGGTTCGTCG GCGGGTCTGA TGGTGGCGGC GGCCCTCGCCG	300
TATGTGGCGT GGATGAGCGT CACCGCGGGG CAGGCCGAGC TGACCGCCGC CCAGGTCCGG	360
GTTGCTGCGG CGGCCTACGA GACGGCGTAT GGGCTGACGG TGCCCCCGCC GGTGATCGCC	420
GAGAACCGTG CTGAACGTGAT GATTCTGATA GCGACCAACC TCTTGGGGCA AAACACCCCG	480
GCGATCGCGG TCAACGAGGC CGAATACGGG GAGATGTGGG CCCAAGACGC CGCCGCGATG	540
TTTGGCTACG CCGCCACGGC GGCGACGGCG ACCGAGGCGT TGCTGCCGTT CGAGGACGCC	600
CCACTGATCA CCAACCCCGG CGGGCTCCTT GAGCAGGCCG TCGCGGTCGA GGAGGCCATC	660
GACACCGCCG CGCGAACCA GTTGATGAAC AATGTGCCCC AAGCGCTGCA ACAACTGGCC	720
CAGCCCACGA AAAGCATCTG GCCGTTGAC CAACTGAGTG AACTCTGGAA AGCCATCTCG	780
CCGCATCTGT CGCCGCTCAG CAACATCGTG TCGATGCTCA ACAACCACGT GTCGATGACC	840
AACTCGGGTG TGTCAATGGC CAGCACCTTG CACTCAATGT TGAAGGGCTT TGCTCCGGCG	900
CGGGCTCAGG CCGTGGAAAC CGCGGCGCAA AACGGGGTCC AGGCGATGAG CTCGCTGGC	960

AGCCAGCTGG GTTCGTCGCT GGGTTCTTCG GGTCTGGCG CTGGGGTGGC CGCCAAC TTG 1020
GGTCGGGC GG CCTCGGTCGG TTCGTTGTCG GTGCCGCAGG CCTGGGCCGC GGCCAACCAG 1080
GCGGTACCC CGGC GGCGCGCG GGCGCTGCC 1109

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 341 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Val Val Asp Phe Gly Ala Leu Pro Pro Glu Ile Asn Ser Ala Arg Met
1 5 10 15

Tyr Ala Gly Pro Gly Ser Ala Ser Leu Val Ala Ala Ala Lys Met Trp
20 25 30

Asp Ser Val Ala Ser Asp Leu Phe Ser Ala Ala Ser Ala Phe Gln Ser
35 40 45

Val Val Trp Gly Leu Thr Thr Gly Ser Trp Ile Gly Ser Ser Ala Gly
50 55 60

Leu Met Val Ala Ala Ala Ser Pro Tyr Val Ala Trp Met Ser Val Thr
65 70 75 80

Ala Gly Gln Ala Glu Leu Thr Ala Ala Gln Val Arg Val Ala Ala Ala
85 90 95

Ala Tyr Glu Thr Ala Tyr Gly Leu Thr Val Pro Pro Pro Val Ile Ala
100 105 110

Glu Asn Arg Ala Glu Leu Met Ile Leu Ile Ala Thr Asn Leu Leu Gly
115 120 125

143

Gln Asn Thr Pro Ala Ile Ala Val Asn Glu Ala Glu Tyr Gly Glu Met
130 135 140

Trp Ala Gln Asp Ala Ala Ala Met Phe Gly Tyr Ala Ala Thr Ala Ala
145 150 155 160

Thr Ala Thr Glu Ala Leu Leu Pro Phe Glu Asp Ala Pro Leu Ile Thr
165 170 175

Asn Pro Gly Gly Leu Leu Glu Gln Ala Val Ala Val Glu Glu Ala Ile
180 185 190

Asp Thr Ala Ala Ala Asn Gln Leu Met Asn Asn Val Pro Gln Ala Leu
195 200 205

Gln Gln Leu Ala Gln Pro Thr Lys Ser Ile Trp Pro Phe Asp Gln Leu
210 215 220

Ser Glu Leu Trp Lys Ala Ile Ser Pro His Leu Ser Pro Leu Ser Asn
225 230 235 240

Ile Val Ser Met Leu Asn Asn His Val Ser Met Thr Asn Ser Gly Val
245 250 255

Ser Met Ala Ser Thr Leu His Ser Met Leu Lys Gly Phe Ala Pro Ala
260 265 270

Ala Ala Gln Ala Val Glu Thr Ala Ala Gln Asn Gly Val Gln Ala Met
275 280 285

Ser Ser Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu
290 295 300

Gly Ala Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser
305 310 315 320

Leu Ser Val Pro Gln Ala Trp Ala Ala Asn Gln Ala Val Thr Pro
325 330 335

Ala Ala Arg Ala Leu
340

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1256 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

CATCGGAGGG AGTGATCACC ATGCTGTGGC ACGCAATGCC ACCGGAGNTA AATACCGCAC	60
GGCTGATGGC CGGCGCGGGT CCGGCTCCAA TGCTTGCAGGC GGCCGCGGGGA TGGCAGACGC	120
TTTCGGCGGC TCTGGACGCT CAGGCCGTCG AGTTGACCGC GCGCCTGAAC TCTCTGGGAG	180
AAGCCTGGAC TGGAGGTGGC AGCGACAAGG CGCTTGCAGGC TGCAACGCCG ATGGTGGTCT	240
GGCTACAAAC CGCGTCAACA CAGGCCAAGA CCCGTGCGAT GCAGGCCGACG GCGCAAGCCG	300
CGGCATACAC CCAGGCCATG GCCACGACGC CGTCGCTGCC GGAGATGCC GCCAACCACA	360
TCACCCAGGC CGTCCTTACG GCCACCAACT TCTTCGGTAT CAACACGATC CCGATCGCGT	420
TGACCGAGAT GGATTATTTG ATCCGTATGT GGAACCAGGC AGCCCTGGCA ATGGAGGTCT	480
ACCAGGCCGA GACCGCGGTT AACACGCTTT TCGAGAAAGCT CGAGGCCATG GCGTCGATCC	540
TTGATCCCGG CGCGAGCCAG AGCACGACGA ACCCGATCTT CGGAATGCC CCCCCCTGGCA	600
GCTAACACCC GGTTGGCCAG TTGCCGCCGG CGGCTACCCA GACCCTGGC CAACTGGGTG	660
AGATGAGCCGG CCCGATGCAG CAGCTGACCC AGCCGCTGCA GCAGGGTACG TCGTTGTTCA	720
GCCAGGTGGG CGGCACCGGC GGCAGCAACC CAGCCGACGA GGAAGCCGCG CAGATGGGCC	780
TGCTCGGCAC CAGTCCGCTG TCGAACCATC CGCTGGCTGG TGGATCAGGC CCCAGCGCGG	840
GCGCGGGCCT GCTGCGCGCG GAGTCGCTAC CTGGCGCAGG TGGGTCGTTG ACCCGCACGC	900
CGCTGATGTC TCAGCTGATC GAAAAGCCGG TTGCCCCCTC GGTGATGCCG GCAGCTGCTG	960
CCGGATCGTC GGCGACGGGT GGCGCCGCTC CGGTGGGTGC GGGAGCGATG GGCCAGGGTG	1020

CGCAATCCGG CGGCTCCACC AGGCCGGTC TGGTCGCGCC GGCACCGCTC GCGCAGGAGC	1080
GTGAAGAAGA CGACGAGGAC GACTGGGACG AAGAGGACGA CTGGTGAGCT CCCGTAATGA	1140
CAACAGACTT CCGGCCACC CGGGCCGGAA GACTTGCCAA CATTGGCG AGGAAGGTA	1200
AGAGAGAAAG TAGTCCAGCA TGGCAGAGAT GAAGACCGAT GCCGCTACCC TCGCGC	1256

(2) INFORMATION FOR SEQ ID NO:113:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 432 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

CTAGTGGATG GGACCATGGC CATTTCTGC AGTCTCACTG CCTTCTGTGT TGACATTTG	60
GCACGCCGGC GGAAACGAAG CACTGGGTC GAAGAACGGC TGCGCTGCCA TATCGTCCGG	120
AGCTTCCATA CCTTCGTGCG GCCGGAAGAG CTTGTCGTAG TCGGCCGCCA TGACAACCTC	180
TCAGAGTGCG CTCAAACGTA TAAACACGAG AAAGGGCGAG ACCGACGGAA GGTCGAACTC	240
GCCCAGATCCC GTGTTTCGCT ATTCTACGCG AACTCGGCGT TGCCCTATGC GAACATCCCA	300
GTGACGTTGC CTTCGGTGCA AGCCATTGCC TGACCGGCTT CGCTGATCGT CCGCGCCAGG	360
TTCTGCAGCG CGTTGTTCAAG CTCGGTAGCC GTGGCGTCCC ATTTTGCTG GACACCCTGG	420
TACGCCTCCG AA	432

(2) INFORMATION FOR SEQ ID NO:114:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 368 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

Met Leu Trp His Ala Met Pro Pro Glu Xaa Asn Thr Ala Arg Leu Met
1 5 10 15

Ala Gly Ala Gly Pro Ala Pro Met Leu Ala Ala Ala Ala Gly Trp Gln
20 25 30

Thr Leu Ser Ala Ala Leu Asp Ala Gln Ala Val Glu Leu Thr Ala Arg
35 40 45

Leu Asn Ser Leu Gly Glu Ala Trp Thr Gly Gly Ser Asp Lys Ala
50 55 60

Leu Ala Ala Ala Thr Pro Met Val Val Trp Leu Gln Thr Ala Ser Thr
65 70 75 80

Gln Ala Lys Thr Arg Ala Met Gln Ala Thr Ala Gln Ala Ala Ala Tyr
85 90 95

Thr Gln Ala Met Ala Thr Thr Pro Ser Leu Pro Glu Ile Ala Ala Asn
100 105 110

His Ile Thr Gln Ala Val Leu Thr Ala Thr Asn Phe Phe Gly Ile Asn
115 120 125

Thr Ile Pro Ile Ala Leu Thr Glu Met Asp Tyr Phe Ile Arg Met Trp
130 135 140

Asn Gln Ala Ala Leu Ala Met Glu Val Tyr Gln Ala Glu Thr Ala Val
145 150 155 160

Asn Thr Leu Phe Glu Lys Leu Glu Pro Met Ala Ser Ile Leu Asp Pro
165 170 175

Gly Ala Ser Gln Ser Thr Thr Asn Pro Ile Phe Gly Met Pro Ser Pro
180 185 190

Gly Ser Ser Thr Pro Val Gly Gln Leu Pro Pro Ala Ala Thr Gln Thr
195 200 205

Leu Gly Gln Leu Gly Glu Met Ser Gly Pro Met Gln Gln Leu Thr Gln
210 215 220

Pro Leu Gln Gln Val Thr Ser Leu Phe Ser Gln Val Gly Gly Thr Gly
225 230 235 240

Gly Gly Asn Pro Ala Asp Glu Glu Ala Ala Gln Met Gly Leu Leu Gly
245 250 255

Thr Ser Pro Leu Ser Asn His Pro Leu Ala Gly Gly Ser Gly Pro Ser
260 265 270

Ala Gly Ala Gly Leu Leu Arg Ala Glu Ser Leu Pro Gly Ala Gly Gly
275 280 285

Ser Leu Thr Arg Thr Pro Leu Met Ser Gln Leu Ile Glu Lys Pro Val
290 295 300

Ala Pro Ser Val Met Pro Ala Ala Ala Gly Ser Ser Ala Thr Gly
305 310 315 320

Gly Ala Ala Pro Val Gly Ala Gly Ala Met Gly Gln Gly Ala Gln Ser
325 330 335

Gly Gly Ser Thr Arg Pro Gly Leu Val Ala Pro Ala Pro Leu Ala Gln
340 345 350

Glu Arg Glu Glu Asp Asp Glu Asp Asp Trp Asp Glu Glu Asp Asp Trp
355 360 365

(2) INFORMATION FOR SEQ ID NO:115:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 12 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

Met Ala Glu Met Lys Thr Asp Ala Ala Thr Leu Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 396 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

GATCTCCGGC GACCTGAAAA CCCAGATCGA CCAGGTGGAG TCGACGGCAG GTTCGTTGCA	60
GGGCCAGTGG CGCGGCGCGG CGGGGACGGC CGCCCAGGCC GCGGTGGTGC GCTTCCAAGA	120
AGCAGCCAAT AAGCAGAACG AGGAACTCGA CGAGATCTCG ACGAATATTG GTCAGGCCGG	180
CGTCCAATAC TCGAGGGCCG ACGAGGAGCA GCAGCAGGCG CTGTCCTCGC AAATGGGCTT	240
CTGACCCGCT AATACGAAAA GAAACGGAGC AAAAACATGA CAGAGCAGCA GTGGAATTTC	300
GCAGGTATCG AGGCCGCGGC AAGCGCAATC CAGGGAAATG TCACGTCCAT TCATTCCCTC	360
CTTGACGAGG GGAAGCAGTC CCTGACCAAG CTCGCA	396

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 80 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

Ile Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala
 1 5 10 15
 Gly Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln
 20 25 30
 Ala Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu
 35 40 45
 Leu Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser
 50 55 60
 Arg Ala Asp Glu Glu Gln Gln Ala Leu Ser Ser Gln Met Gly Phe
 65 70 75 80

(2) INFORMATION FOR SEQ ID NO:118:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 387 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

GTGGATCCCG ATCCCGTGTGTT TCGCTATTCT ACGCGAACTC GGCGTTGCC	TATGCGAAC	60
TCCCCAGTGAC GTTGCCCTTCG GTCGAAGCCA TTGCCTGACC GGCTTCGCTG	ATCGTCCGCG	120
CCAGGTTCTG CAGCGCGTTG TTCAGCTCGG TAGCCGTGGC GTCCCATTTT	TGCTGGACAC	180
CCTGGTACGC CTCCGAACCG CTACCGCCCC AGGCCGCTGC GAGCTTGGTC	AGGGACTGCT	240
TCCCCCTCGTC AAGGAGGGAA TGAATGGACG TGACATTTCC CTGGATTGCG	CTTGCCGCGG	300
CCTCGATAACC CGCGAAATTCA CACTGCTGCT CTGTCATGTT TTTGCTCCGT	TTCTTTTCGT	360
ATTAGCGGGT CAGAAGCCCA TTTGCGA		387

150

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 272 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

CGGCACGAGG ATCTCGGTTG GCCCAACGGC GCTGGCGAGG GCTCCGTTCC GGGGGCGAGC	60
TGCGCGCCGG ATGCTTCCTC TGCCCCAGC CGCGCCTGGA TGGATGGACC AGTTGCTACC	120
TTCCCGACGT TTCGTTCGGT GTCTGTGCGA TAGCGGTGAC CCCGGCGCGC ACGTCGGGAG	180
TGTTGGGGGG CAGGCCGGGT CGGTGGTTCG GCCGGGGACG CAGACGGTCT GGACGGAACG	240
GGCGGGGGTT CGCCGATTGG CATCTTGCC CA	272

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

Asp Pro Val Asp Ala Val Ile Asn Thr Thr Cys Asn Tyr Gly Gln Val			
1	5	10	15
Val Ala Ala Leu			
20			

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Ala Val Glu Ser Gly Met Leu Ala Leu Gly Thr Pro Ala Pro Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala Ala Lys
1 5 10 15

Glu Gly Arg

(2) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Tyr Tyr Trp Cys Pro Gly Gln Pro Phe Asp Pro Ala Trp Gly Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Asp Ile Gly Ser Glu Ser Thr Glu Asp Gln Gln Xaa Ala Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Ala Glu Glu Ser Ile Ser Thr Xaa Glu Xaa Ile Val Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Asp Pro Glu Pro Ala Pro Pro Val Pro Thr Thr Ala Ala Ser Pro Pro
1 5 10 15
Ser

(2) INFORMATION FOR SEO ID NO:127:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Ala Pro Lys Thr Tyr Xaa Glu Glu Leu Lys Gly Thr Asp Thr Gly
1 5 10 15

(2) INFORMATION FOR SEO ID NO. 128:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln Leu Thr Ser
1 5 10 15

Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala Asn
20 25 30

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Asp Pro Pro Asp Pro His Gln Xaa Asp Met Thr Lys Gly Tyr Tyr Pro
1 5 10 15

Gly Gly Arg Arg Xaa Phe
20

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Asp Pro Gly Tyr Thr Pro Gly
1 5

(2) INFORMATION FOR SEQ ID NO:131:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: /note= "The Second Residue Can Be Either a Pro or Thr"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

Xaa	Xaa	Gly	Phe	Thr	Gly	Pro	Gln	Phe	Tyr
1				5				10	

(2) INFORMATION FOR SEQ ID NO:132:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 9 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: /note= "The Third Residue Can Be Either a Gln or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

Xaa	Pro	Xaa	Val	Thr	Ala	Tyr	Ala	Gly
1				5				

(2) INFORMATION FOR SEQ ID NO:133:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 9 amino acids

- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

Xaa Xaa Xaa Glu Lys Pro Phe Leu Arg
1 5

(2) INFORMATION FOR SEQ ID NO:134:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

Xaa Asp Ser Glu Lys Ser Ala Thr Ile Lys Val Thr Asp Ala Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:135:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

Ala Gly Asp Thr Xaa Ile Tyr Ile Val Gly Asn Leu Thr Ala Asp

1

5

10

15

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

Ala	Pro	Glu	Ser	Gly	Ala	Gly	Leu	Gly	Gly	Thr	Val	Gln	Ala	Gly
1					5					10			15	

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Xaa	Tyr	Ile	Ala	Tyr	Xaa	Thr	Thr	Ala	Gly	Ile	Val	Pro	Gly	Lys	Ile
1					5					10			15		

Asn	Val	His	Leu	Val
			20	

Claims

1. A polypeptide comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 121)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 123)
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val; (SEQ ID No. 124)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser; (SEQ ID No. 126)
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly; (SEQ ID No. 127)
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128) and
- (j) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)

wherein Xaa may be any amino acid.

2. A polypeptide comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative

substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

- 1 (a) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129) and
(b) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 137), wherein Xaa may be any amino acid.

3. A polypeptide comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101 or a complement thereof under moderately stringent conditions.

4. A polypeptide comprising an immunogenic portion of a *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 26-51, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 26-51 or a complement thereof under moderately stringent conditions.

5. A DNA molecule comprising a nucleotide sequence encoding a polypeptide according to any one of claims 1-4.

6. An expression vector comprising a DNA molecule according to claim 5.

7. A host cell transformed with an expression vector according to claim 6.

8. The host cell of claim 7 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cells.

9. A pharmaceutical composition comprising one or more polypeptides according to any one of claims 1-4 and a physiologically acceptable carrier.

10. A pharmaceutical composition comprising one or more DNA molecules according to claim 5 and a physiologically acceptable carrier.

11. A pharmaceutical composition comprising one or more DNA sequences recited in SEQ ID Nos.: 3, 11 and 12; and a physiologically acceptable carrier.

12. A vaccine comprising one or more polypeptides according to any one of claims 1-4 and a non-specific immune response enhancer.

13. A vaccine comprising:

a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and

a non-specific immune response enhancer.

14. A vaccine comprising:

one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and

a non-specific immune response enhancer.

15. The vaccine of claims 12-14 wherein the non-specific immune response enhancer is an adjuvant.

16. A vaccine comprising one or more DNA molecules according to claim 5 and a non-specific immune response enhancer.

17. A vaccine comprising one or more DNA sequences recited in SEQ ID Nos.: 3, 11 and 12; and a non-specific immune response enhancer.

18. The vaccine of claims 16 or 17 wherein the non-specific immune response enhancer is an adjuvant.

19. A method for inducing protective immunity in a patient, comprising administering to a patient a pharmaceutical composition according to any one of claims 9-11.

20. A method for inducing protective immunity in a patient, comprising administering to a patient a vaccine according to any one of claims 12-18.

21. A fusion protein comprising two or more polypeptides according to any one of claims 1-4.

22. A fusion protein comprising one or more polypeptides according to any one of claims 1-4 and ESAT-6.

23. A pharmaceutical composition comprising a fusion protein according to claim 21 or 22 and a physiologically acceptable carrier.

24. A vaccine comprising a fusion protein according to claims 21 or 22 and a non-specific immune response enhancer.

25. The vaccine of claim 24 wherein the non-specific immune response enhancer is an adjuvant.

26. A method for inducing protective immunity in a patient, comprising administering to a patient a pharmaceutical composition according to claim 23.

27. A method for inducing protective immunity in a patient, comprising administering to a patient a vaccine according to claims 24 or 25.

28. A method for detecting tuberculosis in a patient, comprising:
 - (a) contacting dermal cells of a patient with one or more polypeptides according to any one of claims 1-4; and
 - (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.
29. A method for detecting tuberculosis in a patient, comprising:
 - (a) contacting dermal cells of a patient with a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and
 - (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.
30. A method for detecting tuberculosis in a patient, comprising:
 - (a) contacting dermal cells of a patient with one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and
 - (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.
31. The method of any one of claims 28-30 wherein the immune response is induration.
32. A diagnostic kit comprising:
 - (a) a polypeptide according to any one of claims 1-4; and
 - (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.

33. A diagnostic kit comprising:

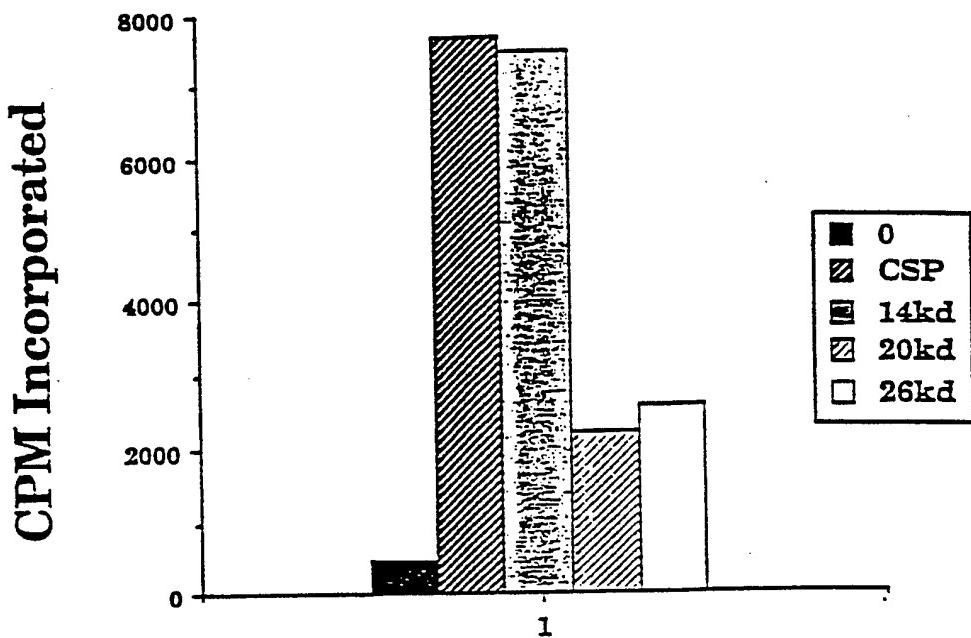
- (a) a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and
- (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.

34. A diagnostic kit comprising:

- (a) a polypeptide encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and
- (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.

1/3

D7 T Cell Proliferation



D7 IFN γ

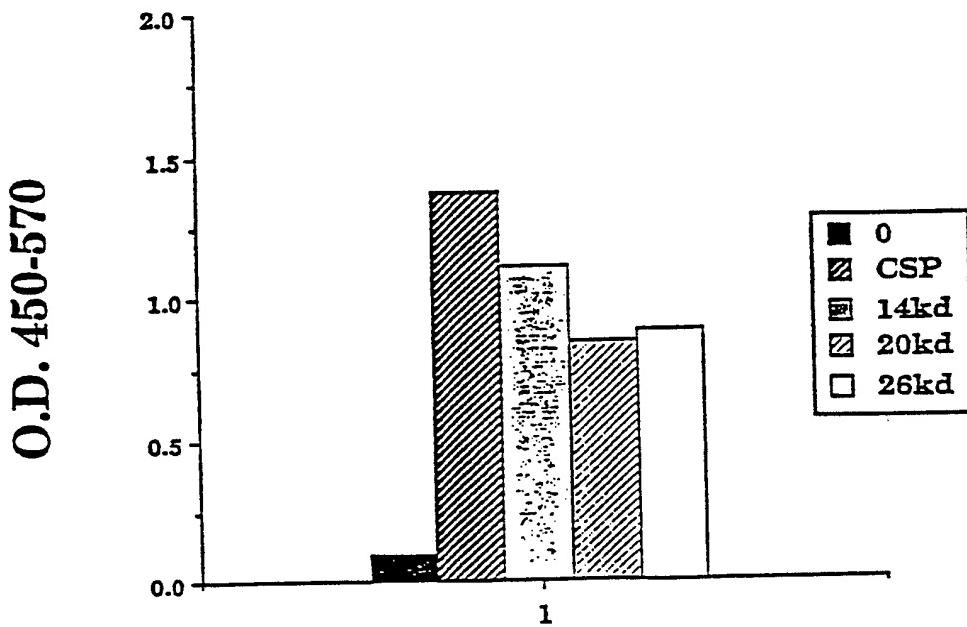
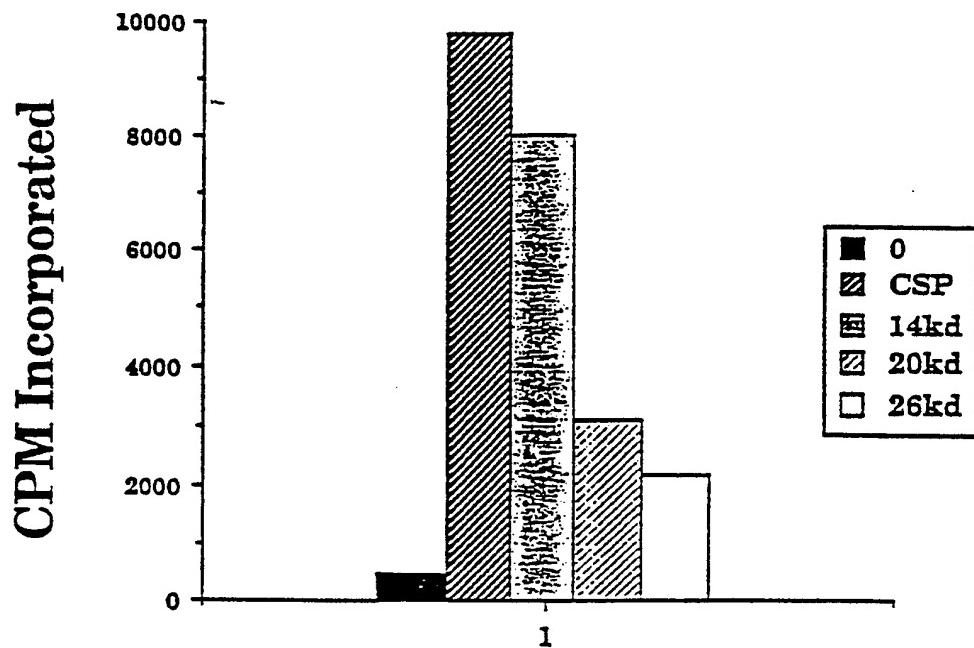


Fig. 1A

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D160 T Cell Proliferation



D160 IFNg

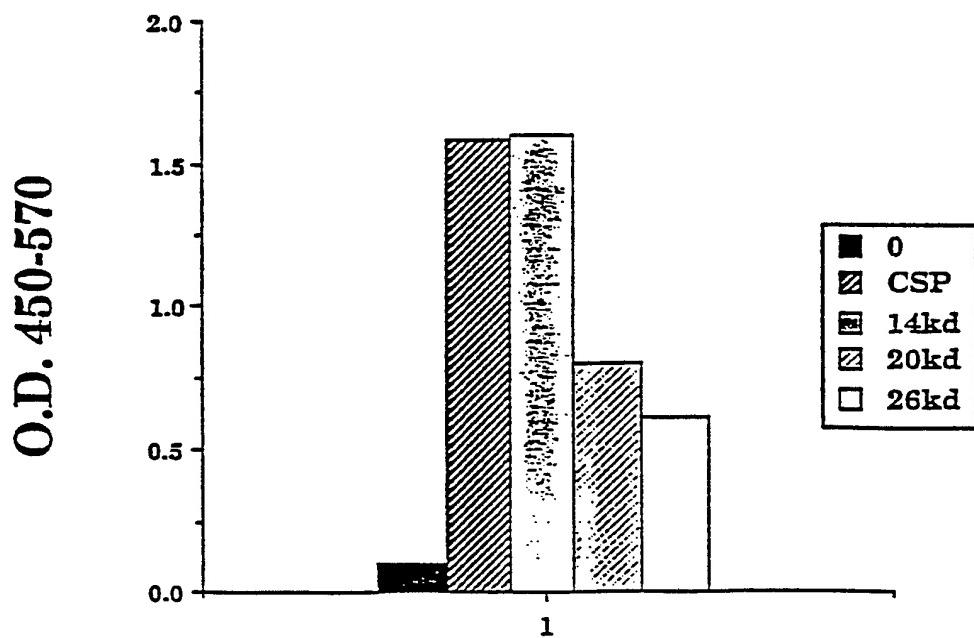


Fig. 1B

3/3

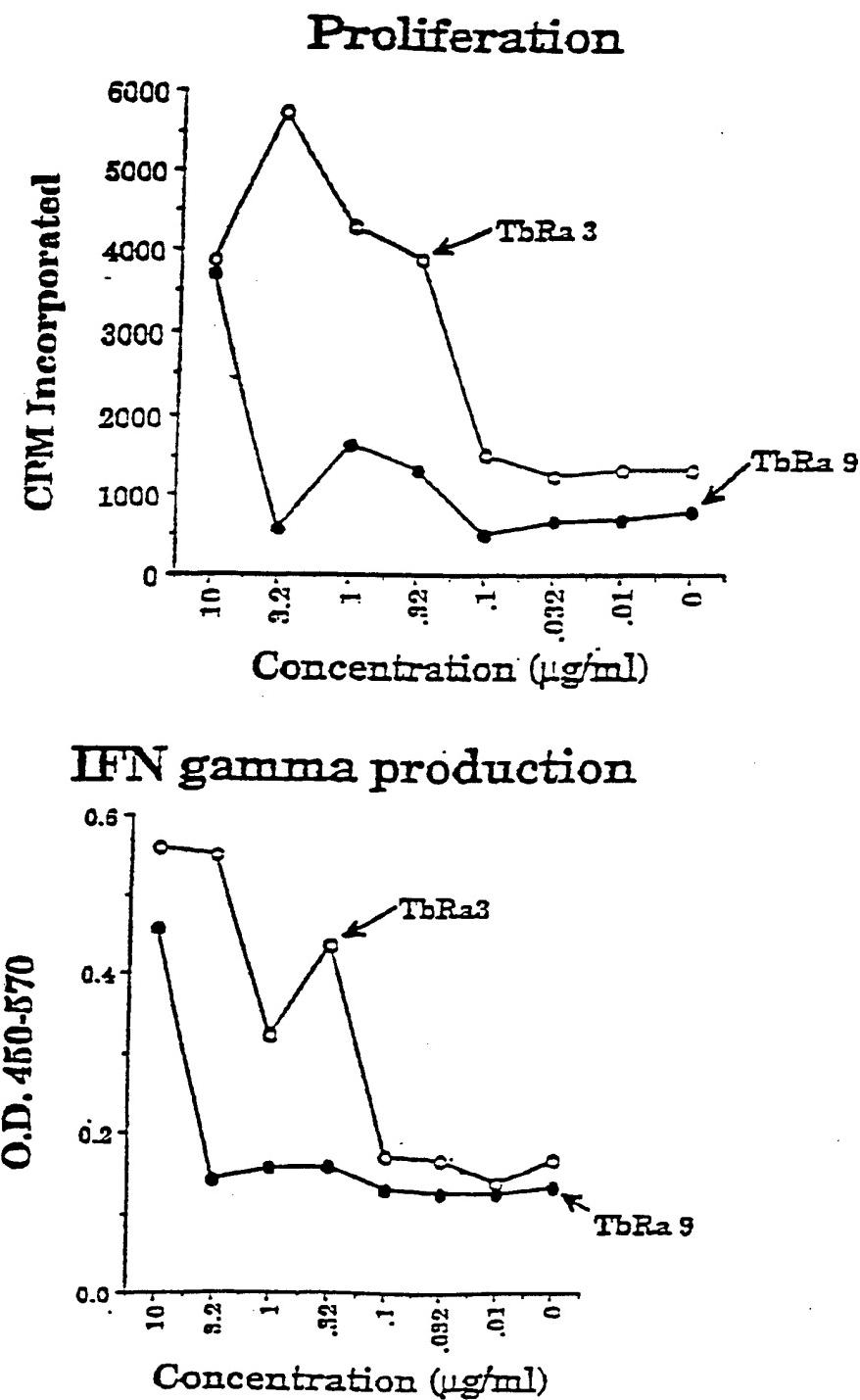


Fig. 2



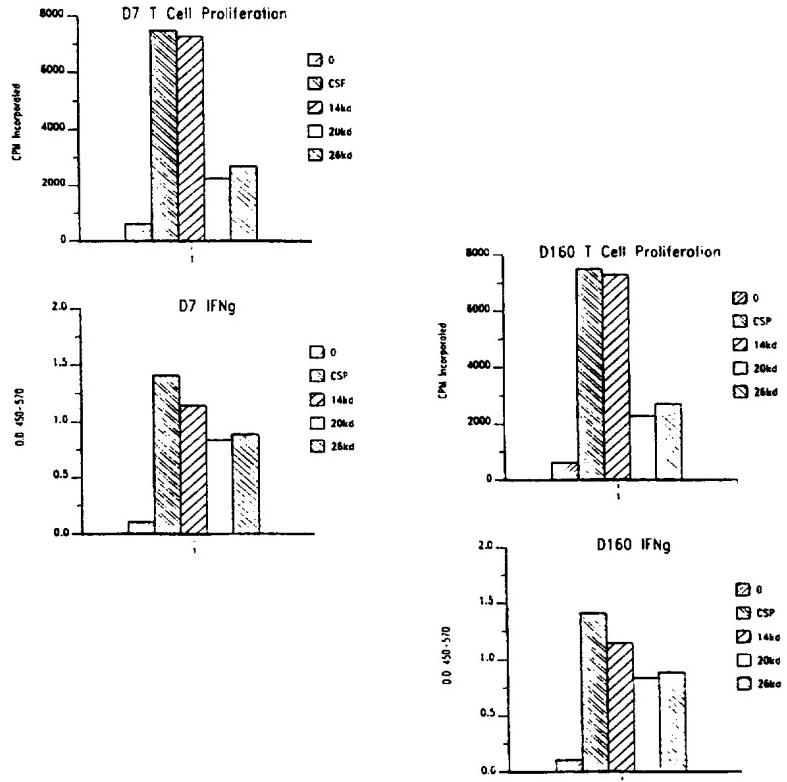
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C12N 15/31, C07K 14/35, A61K 38/16, C12N 15/62, G01N 33/569, C12Q 1/68, C12N 5/10, 1/21 // A61K 39/04, (C12N 1/21, C12R 1:19)		(43) International Publication Date: 13 March 1997 (13.03.97)
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(22) International Filing Date: 30 August 1996 (30.08.96)	(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
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08/680,574 12 July 1996 (12.07.96) US		
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(72) Inventors: REED, Steven, G.; 2843 - 122nd Pine Place N.E., Bellevue, WA 98005 (US). SKEIKY, Yasir, A., W.; 8327 - 25th Avenue N.W., Seattle, WA 98117 (US). DILLON, Davin, C.; 21607 N.E. 24th Street, Redmond, WA 98053 (US). CAMPOS-NETO, Antonio; 9308 N.E. Midship Court, Bainbridge Island, WA 98110 (US). HOUGHTON, Raymond; 2636 - 242nd Place S.E., Bothell, WA 98021 (US). VEDVICK, Thomas, H.; 1301 Spring Street, Seattle, WA 98104 (US). TWARDZIK, Daniel, R.; 10195 South Beach Drive, Bainbridge Island, WA 98110 (US).	(88) Date of publication of the international search report: 17 July 1997 (17.07.97)	

(54) Title: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND DIAGNOSIS OF TUBERCULOSIS

(57) Abstract

Compounds and methods for inducing protective immunity against tuberculosis are disclosed. The compounds provided include polypeptides that contain at least one immunogenic portion of one or more *M. tuberculosis* proteins and DNA molecules encoding such polypeptides. Such compounds may be formulated into vaccines and/or pharmaceutical compositions for immunization against *M. tuberculosis* infection, or may be used for the diagnosis of tuberculosis.



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/14674

A. CLASSIFICATION OF SUBJECT MATTER			
IPC 6	C12N15/31	C07K14/35	A61K38/16
	C12Q1/68	C12N5/10	C12N1/21
	(C12N1/21, C12R1:19)		
			C12N15/62 G01N33/569
			//A61K39/04,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 95 01440 A (STATENS SERUMINSTITUT ; HASLOEV KAARE (DK); ANDERSEN AASE BENGAARD) 12 January 1995</p> <p>see abstract</p> <p>see page 1, line 1-30</p> <p>see page 4, line 8-31</p> <p>see page 6, line 22 - page 7, line 21</p> <p>see page 11, line 18 - page 12, line 31</p> <p>see page 17, line 8-24</p> <p>see page 24, line 18-25; figure 1</p> <p>see page 36 - page 43; examples 2-5</p> <p>see claims</p> <p>---</p> <p>-/-</p>	1,3-9, 12,15, 19,20, 28,31,32

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Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 1997	04. 06. 97

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Fax (+ 31-70) 340-3016

Authorized officer

Macchia, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/14674

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 01441 A (STATENS SERUMSINSTITUT ;ANDERSEN PETER (DK); ANDERSEN AASE BENGAAR) 12 January 1995 see abstract see page 9, line 3 - page 20, line 31 see page 25, line 1-25 see page 32, line 6 - page 35, line 6 see claims ---	1,3-10, 12,15, 16,18, 22-27
A	VACCINE, vol. 12, no. 16, 1994, pages 1537-1540, XP002026338 LOWRIE ET AL.: "Towards a DNA vaccine against tuberculosis" see abstract see page 1539, left-hand column, paragraph 4 ---	10,16,18
A	INFECTION AND IMMUNITY, vol. 57, no. 1, January 1989, pages 283-288, XP002026408 YAMAGUCHI ET AL.: "Cloning and characterization of the gene for immunogenic protein MpB64 of mycobacterium bovis BCG" ---	
A	ANN. INST. PASTEUR/MICROBIOL., vol. 136B, 1985, pages 235-248, XP002026409 ROMAIN ET AL.: "Preparation of Tuberculin antigen L" ---	
A	WO 92 21758 A (PASTEUR INSTITUT) 10 December 1992 ---	
A	AUSUBEL ET AL.: "Current Protocols in Molecular Biology" 1993 , WILEY & SONS , US, NEW YORK XP002026411 see page 10.19.1 - page 10.19.12 ---	
A	INFECTION AND IMMUNITY, vol. 55, no. 6, June 1987, pages 1421-1425, XP002026410 YOUNG ET AL.: "Screening of a recombinant mycobacterial DNA library with polyclonal antiserum and molecular weight analysis of expressed antigens" ---	
1	WO 94 00493 A (KAPOOR ARCHANA ;MUNSHI ANIL (US)) 6 January 1994 -----	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/14674

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **19, 20, 26-28, 31**
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although these claims are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

51 inventions * see continuation-sheets PCT/ISA/210 *

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 3-10, 12, 15, 16, 18-28, 31, 32 all partially**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14674

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

- 1) claims 1, 3-10, 12, 15, 16, 18-28, 31, 32 all partially:
a polypeptide comprising an immunogenic portion of a soluble M. tuberculosis antigen or a variant, having an N-terminal aminoacid sequence as in Seq. ID:120, a DNA molecule encoding said polypeptide as in Seq. ID:101, overlapping or adjacent DNA molecule as in Seq. ID:31, 32, 33, 51 and encoded polypeptides, an expression vector comprising said DNA molecules, an host transformed with said expression vector, pharmaceutical and vaccine compositions comprising said polypeptides or said DNA molecules, fusion protein comprising said polypeptides, a diagnostic kit comprising said polypeptides.
- 2) claims 1, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:121.
- 3) claims 1, 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:122 and 25.
- 4) claims 1, 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:123 and 24.
- 5) claims 1, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:124.
- 6) claims 1, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:125.
- 7) claims 1, 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:126 and 52.
- 8) claims 1, 5-12, 14-28, 30-32, 34 all partially:
same as invention 1 but for Seq. ID:127 and 3.
- 9) claims 1, 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:128, 99, 1 and 21.
- 10) claims 1, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:136.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14674

FURTHER INFORMATION CONTINUED FROM PCT/USA/210

11) claims 2, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:129.

12) claims 2, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:137.

13) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:2.

14) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:4 and 17.

15) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:5, 14 and 18.

16) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:6.

17) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:7.

18) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:8.

19) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:9.

20) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:10 and 13.

21) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:15.

22) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:16.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14674

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

23) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:19.

24) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:20.

25) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:22.

26) claims 3, 5-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:23.

27) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:26.

28) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:27.

29) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:28.

30) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:29.

31) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:30.

32) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:34.

33) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:35.

34) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:36.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14674

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

35) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:37.

36) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:38.

37) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:39.

38) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:40.

39) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:41.

40) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:42.

41) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:43 and 44.

42) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:45.

43) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:46.

44) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:47.

45) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:48.

46) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:49.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 14674

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

47) claims 4-10, 12, 15, 16, 18-28, 31, 32 all partially:
same as invention 1 but for Seq. ID:50.

48) claims 11, 14, 15, 17-20, 30, 31, 34 all partially:
pharmaceutical and vaccine compositions comprising a DNA molecule as
in Seq. ID:11 or the encoded polypeptide, a diagnostic kit comprising said
polypeptide.

49) claims 11, 14, 15, 17-20, 30, 31, 34 all partially:
same as invention 50 but for Seq. ID:12.

50) claims 13, 15, 20, 29, 31, 33 all partially:
vaccine comprising a polypeptide whose N-terminal sequence is as Seq.
ID:134, a diagnostic kit comprising said polypeptide.

51) claims 13, 15, 20, 29, 31, 33 all partially:
same as invention 52 but for Seq. ID:135.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/14674

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WO 9501441 A	12-01-95	AU 7068894 A CA 2165949 A EP 0706571 A	24-01-95 12-01-95 17-04-96
WO 9221758 A	10-12-92	FR 2677365 A CA 2110389 A EP 0589943 A JP 6508513 T	11-12-92 10-12-92 06-04-94 29-09-94
WO 9400493 A	06-01-94	US 5330754 A AU 4651193 A EP 0649435 A JP 7508649 T US 5559011 A	19-07-94 24-01-94 26-04-95 28-09-95 24-09-96



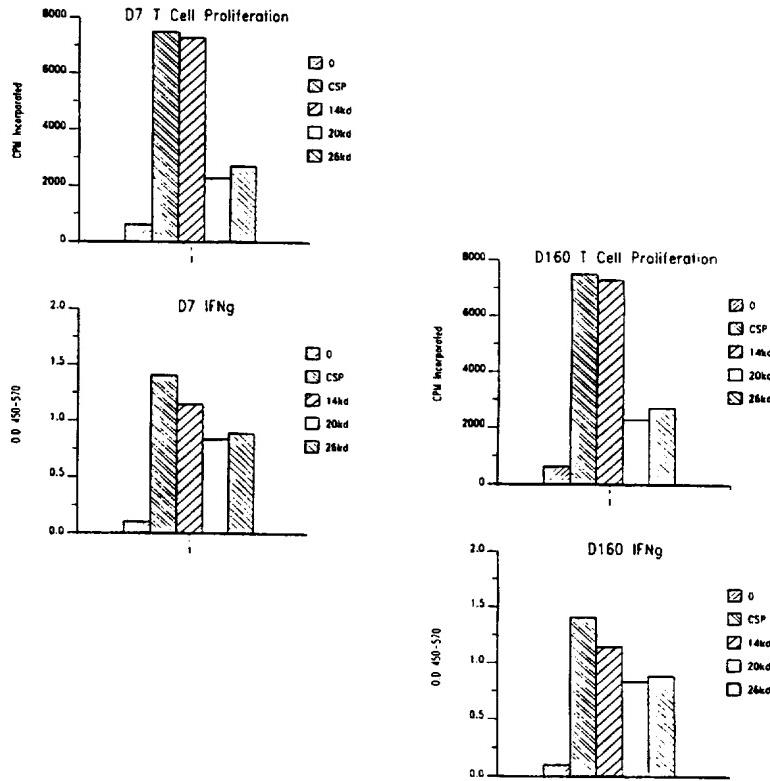
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C12N 15/31, C07K 14/35, A61K 38/16, C12N 15/62, G01N 33/569, C12Q 1/68, C12N 5/10, 1/21 // A61K 39/04, (C12N 1/21, 1:19)		(43) International Publication Date: 13 March 1997 (13.03.97)
(21) International Application Number: PCT/US96/14674		(74) Agents: MAKI, David, J. et al.; Seed and Berry L.L.P., 6300 Columbia Center, 701 Fifth Avenue, Seattle, WA 98104-7092 (US).
(22) International Filing Date: 30 August 1996 (30.08.96)		(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(30) Priority Data:		
08/523,436 1 September 1995 (01.09.95) US		
08/533,634 22 September 1995 (22.09.95) US		
08/620,874 22 March 1996 (22.03.96) US		
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(54) Title: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND DIAGNOSIS OF TUBERCULOSIS

(57) Abstract

Compounds and methods for inducing protective immunity against tuberculosis are disclosed. The compounds provided include polypeptides that contain at least one immunogenic portion of one or more *M. tuberculosis* proteins and DNA molecules encoding such polypeptides. Such compounds may be formulated into vaccines and/or pharmaceutical compositions for immunization against *M. tuberculosis* infection, or may be used for the diagnosis of tuberculosis.



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Description

5

COMPOUNDS AND METHODS FOR IMMUNOTHERAPY
AND DIAGNOSIS OF TUBERCULOSISTechnical Field

10 The present invention relates generally to detecting, treating and preventing *Mycobacterium tuberculosis* infection. The invention is more particularly related to polypeptides comprising a *Mycobacterium tuberculosis* antigen, or a portion or other variant thereof, and the use of such polypeptides for diagnosing and vaccinating against *Mycobacterium tuberculosis* infection.

15

Background of the Invention

Tuberculosis is a chronic, infectious disease, that is generally caused by infection with *Mycobacterium tuberculosis*. It is a major disease in developing countries, as well as an increasing problem in developed areas of the world, with about

20 8 million new cases and 3 million deaths each year. Although the infection may be asymptomatic for a considerable period of time, the disease is most commonly manifested as an acute inflammation of the lungs, resulting in fever and a nonproductive cough. If left untreated, serious complications and death typically result.

Although tuberculosis can generally be controlled using extended
25 antibiotic therapy, such treatment is not sufficient to prevent the spread of the disease. Infected individuals may be asymptomatic, but contagious, for some time. In addition,

although compliance with the treatment regimen is critical, patient behavior is difficult to monitor. Some patients do not complete the course of treatment, which can lead to ineffective treatment and the development of drug resistance.

Inhibiting the spread of tuberculosis requires effective vaccination and accurate, early diagnosis of the disease. Currently, vaccination with live bacteria is the most efficient method for inducing protective immunity. The most common Mycobacterium employed for this purpose is *Bacillus Calmette-Guerin* (BCG), an avirulent strain of *Mycobacterium bovis*. However, the safety and efficacy of BCG is a source of controversy and some countries, such as the United States, do not vaccinate the general public. Diagnosis is commonly achieved using a skin test, which involves intradermal exposure to tuberculin PPD (protein-purified derivative). Antigen-specific T cell responses result in measurable induration at the injection site by 48-72 hours after injection, which indicates exposure to Mycobacterial antigens. Sensitivity and specificity have, however, been a problem with this test, and individuals vaccinated with BCG cannot be distinguished from infected individuals.

While macrophages have been shown to act as the principal effectors of *M. tuberculosis* immunity, T cells are the predominant inducers of such immunity. The essential role of T cells in protection against *M. tuberculosis* infection is illustrated by the frequent occurrence of *M. tuberculosis* in AIDS patients, due to the depletion of CD4 T cells associated with human immunodeficiency virus (HIV) infection. Mycobacterium-reactive CD4 T cells have been shown to be potent producers of gamma-interferon (IFN- γ), which, in turn, has been shown to trigger the anti-mycobacterial effects of macrophages in mice. While the role of IFN- γ in humans is less clear, studies have shown that 1,25-dihydroxy-vitamin D3, either alone or in combination with IFN- γ or tumor necrosis factor-alpha, activates human macrophages to inhibit *M. tuberculosis* infection. Furthermore, it is known that IFN- γ stimulates human macrophages to make 1,25-dihydroxy-vitamin D3. Similarly, IL-12 has been shown to play a role in stimulating resistance to *M. tuberculosis* infection. For a review of the immunology of *M. tuberculosis* infection see Chan and Kaufmann in

Tuberculosis: Pathogenesis, Protection and Control, Bloom (ed.), ASM Press, Washington, DC, 1994.

Accordingly, there is a need in the art for improved vaccines and methods for preventing, treating and detecting tuberculosis. The present invention 5 fulfills these needs and further provides other related advantages.

Summary of the Invention

Briefly stated, this invention provides compounds and methods for preventing and diagnosing tuberculosis. In one aspect, polypeptides are provided 10 comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications. In one embodiment of this aspect, the soluble antigen has one of the following N-terminal sequences:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-
15 Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-
Ser; (SEQ ID No. 121)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-
Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- 20 (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-
Pro; (SEQ ID No. 123)
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val;
(SEQ ID No. 124)
- 25 (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID
No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-
Pro-Pro-Ser; (SEQ ID No. 126)
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-
Gly; (SEQ ID No. 127)

- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128)
- 5 (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) or
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)

10 wherein Xaa may be any amino acid.

In a related aspect, polypeptides are provided comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, the antigen having one of the following N-terminal sequences:

- 15 (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 137) or
- (n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129)

wherein Xaa may be any amino acid.

20 In another embodiment, the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101 or a complement thereof under moderately stringent
25 conditions.

In a related aspect, the polypeptides comprise an immunogenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that differs only in conservative substitutions and/or modifications, wherein the antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of
30 the sequences recited in SEQ ID Nos.: 26-51, the complements of said sequences, and

DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 26-51 or a complement thereof under moderately stringent conditions.

In related aspects, DNA sequences encoding the above polypeptides, expression vectors comprising these DNA sequences and host cells transformed or
5 transfected with such expression vectors are also provided.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known *M. tuberculosis* antigen.

Within other aspects, the present invention provides pharmaceutical
10 compositions that comprise one or more of the above polypeptides, or a DNA molecule encoding such polypeptides, and a physiologically acceptable carrier. The invention also provides vaccines comprising one or more of the polypeptides as described above and a non-specific immune response enhancer, together with vaccines comprising one or more DNA sequences encoding such polypeptides and a non-specific immune
15 response enhancer.

In yet another aspect, methods are provided for inducing protective immunity in a patient, comprising administering to a patient an effective amount of one or more of the above polypeptides.

In further aspects of this invention, methods and diagnostic kits are
20 provided for detecting tuberculosis in a patient. The methods comprise contacting dermal cells of a patient with one or more of the above polypeptides and detecting an immune response on the patient's skin. The diagnostic kits comprise one or more of the above polypeptides in combination with an apparatus sufficient to contact the polypeptide with the dermal cells of a patient.

25 These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

Brief Description of the Drawings and Sequence Identifiers

Figure 1A and B illustrate the stimulation of proliferation and interferon- γ production in T cells derived from a first and a second *M. tuberculosis*-immune donor, respectively, by the 14 Kd, 20 Kd and 26 Kd antigens described in Example 1.

5 Figure 2 illustrates the stimulation of proliferation and interferon- γ production in T cells derived from an *M. tuberculosis*-immune individual by the two representative polypeptides TbRa3 and TbRa9.

- SEQ. ID NO. 1 is the DNA sequence of TbRa1.
10 SEQ. ID NO. 2 is the DNA sequence of TbRa10.
 SEQ. ID NO. 3 is the DNA sequence of TbRa11.
 SEQ. ID NO. 4 is the DNA sequence of TbRa12.
 SEQ. ID NO. 5 is the DNA sequence of TbRa13.
 SEQ. ID NO. 6 is the DNA sequence of TbRa16.
15 SEQ. ID NO. 7 is the DNA sequence of TbRa17.
 SEQ. ID NO. 8 is the DNA sequence of TbRa18.
 SEQ. ID NO. 9 is the DNA sequence of TbRa19.
 SEQ. ID NO. 10 is the DNA sequence of TbRa24.
 SEQ. ID NO. 11 is the DNA sequence of TbRa26.
20 SEQ. ID NO. 12 is the DNA sequence of TbRa28.
 SEQ. ID NO. 13 is the DNA sequence of TbRa29.
 SEQ. ID NO. 14 is the DNA sequence of TbRa2A.
 SEQ. ID NO. 15 is the DNA sequence of TbRa3.
 SEQ. ID NO. 16 is the DNA sequence of TbRa32.
25 SEQ. ID NO. 17 is the DNA sequence of TbRa35.
 SEQ. ID NO. 18 is the DNA sequence of TbRa36.
 SEQ. ID NO. 19 is the DNA sequence of TbRa4.
 SEQ. ID NO. 20 is the DNA sequence of TbRa9.
 SEQ. ID NO. 21 is the DNA sequence of TbRaB.
30 SEQ. ID NO. 22 is the DNA sequence of TbRaC.

- SEQ. ID NO. 23 is the DNA sequence of TbRaD.
- SEQ. ID NO. 24 is the DNA sequence of YYWCPG.
- SEQ. ID NO. 25 is the DNA sequence of AAMK.
- SEQ. ID NO. 26 is the DNA sequence of TbL-23.
- 5 SEQ. ID NO. 27 is the DNA sequence of TbL-24.
- SEQ. ID NO. 28 is the DNA sequence of TbL-25.
- SEQ. ID NO. 29 is the DNA sequence of TbL-28.
- SEQ. ID NO. 30 is the DNA sequence of TbL-29.
- 10 SEQ. ID NO. 31 is the DNA sequence of TbH-5.
- SEQ. ID NO. 32 is the DNA sequence of TbH-8.
- SEQ. ID NO. 33 is the DNA sequence of TbH-9.
- SEQ. ID NO. 34 is the DNA sequence of TbM-1.
- SEQ. ID NO. 35 is the DNA sequence of TbM-3.
- SEQ. ID NO. 36 is the DNA sequence of TbM-6.
- 15 SEQ. ID NO. 37 is the DNA sequence of TbM-7.
- SEQ. ID NO. 38 is the DNA sequence of TbM-9.
- SEQ. ID NO. 39 is the DNA sequence of TbM-12.
- SEQ. ID NO. 40 is the DNA sequence of TbM-13.
- SEQ. ID NO. 41 is the DNA sequence of TbM-14.
- 20 SEQ. ID NO. 42 is the DNA sequence of TbM-15.
- SEQ. ID NO. 43 is the DNA sequence of TbH-4.
- SEQ. ID NO. 44 is the DNA sequence of TbH-4-FWD.
- SEQ. ID NO. 45 is the DNA sequence of TbH-12.
- SEQ. ID NO. 46 is the DNA sequence of Tb38-1.
- 25 SEQ. ID NO. 47 is the DNA sequence of Tb38-4.
- SEQ. ID NO. 48 is the DNA sequence of TbL-17.
- SEQ. ID NO. 49 is the DNA sequence of TbL-20.
- SEQ. ID NO. 50 is the DNA sequence of TbL-21.
- SEQ. ID NO. 51 is the DNA sequence of TbH-16.
- 30 SEQ. ID NO. 52 is the DNA sequence of DPEP.

SEQ. ID NO. 53 is the deduced amino acid sequence of DPEP.

SEQ. ID NO. 54 is the protein sequence of DPV N-terminal Antigen.

SEQ. ID NO. 55 is the protein sequence of AVGS N-terminal Antigen.

SEQ. ID NO. 56 is the protein sequence of AAMK N-terminal Antigen.

5 SEQ. ID NO. 57 is the protein sequence of YYWC N-terminal Antigen.

SEQ. ID NO. 58 is the protein sequence of DIGS N-terminal Antigen.

SEQ. ID NO. 59 is the protein sequence of AEES N-terminal Antigen.

SEQ. ID NO. 60 is the protein sequence of DPEP N-terminal Antigen.

SEQ. ID NO. 61 is the protein sequence of APK T N-terminal Antigen.

10 SEQ. ID NO. 62 is the protein sequence of DPAS N-terminal Antigen.

SEQ. ID NO. 63 is the deduced amino acid sequence of TbRa1.

SEQ. ID NO. 64 is the deduced amino acid sequence of TbRa10.

SEQ. ID NO. 65 is the deduced amino acid sequence of TbRa11.

SEQ. ID NO. 66 is the deduced amino acid sequence of TbRa12.

15 SEQ. ID NO. 67 is the deduced amino acid sequence of TbRa13.

SEQ. ID NO. 68 is the deduced amino acid sequence of TbRa16.

SEQ. ID NO. 69 is the deduced amino acid sequence of TbRa17.

SEQ. ID NO. 70 is the deduced amino acid sequence of TbRa18.

SEQ. ID NO. 71 is the deduced amino acid sequence of TbRa19.

20 SEQ. ID NO. 72 is the deduced amino acid sequence of TbRa24.

SEQ. ID NO. 73 is the deduced amino acid sequence of TbRa26.

SEQ. ID NO. 74 is the deduced amino acid sequence of TbRa28.

SEQ. ID NO. 75 is the deduced amino acid sequence of TbRa29.

SEQ. ID NO. 76 is the deduced amino acid sequence of TbRa2A.

25 SEQ. ID NO. 77 is the deduced amino acid sequence of TbRa3.

SEQ. ID NO. 78 is the deduced amino acid sequence of TbRa32.

SEQ. ID NO. 79 is the deduced amino acid sequence of TbRa35.

SEQ. ID NO. 80 is the deduced amino acid sequence of TbRa36.

SEQ. ID NO. 81 is the deduced amino acid sequence of TbRa4.

30 SEQ. ID NO. 82 is the deduced amino acid sequence of TbRa9.

- SEQ. ID NO. 83 is the deduced amino acid sequence of TbRaB.
- SEQ. ID NO. 84 is the deduced amino acid sequence of TbRaC.
- SEQ. ID NO. 85 is the deduced amino acid sequence of TbRaD.
- SEQ. ID NO. 86 is the deduced amino acid sequence of YYWCPG.
- 5 SEQ. ID NO. 87 is the deduced amino acid sequence of TbAAMK.
- SEQ. ID NO. 88 is the deduced amino acid sequence of Tb38-1.
- SEQ. ID NO. 89 is the deduced amino acid sequence of TbH-4.
- SEQ. ID NO. 90 is the deduced amino acid sequence of TbH-8.
- SEQ. ID NO. 91 is the deduced amino acid sequence of TbH-9.
- 10 SEQ. ID NO. 92 is the deduced amino acid sequence of TbH-12.
- SEQ. ID NO. 93 is the amino acid sequence of Tb38-1 Peptide 1.
- SEQ. ID NO. 94 is the amino acid sequence of Tb38-1 Peptide 2.
- SEQ. ID NO. 95 is the amino acid sequence of Tb38-1 Peptide 3.
- SEQ. ID NO. 96 is the amino acid sequence of Tb38-1 Peptide 4.
- 15 SEQ. ID NO. 97 is the amino acid sequence of Tb38-1 Peptide 5.
- SEQ. ID NO. 98 is the amino acid sequence of Tb38-1 Peptide 6.
- SEQ. ID NO. 99 is the DNA sequence of DPAS.
- SEQ. ID NO. 100 is the deduced amino acid sequence of DPAS.
- SEQ. ID NO. 101 is the DNA sequence of DPV.
- 20 SEQ. ID NO. 102 is the deduced amino acid sequence of DPV.
- SEQ. ID NO. 103 is the DNA sequence of ESAT-6.
- SEQ. ID NO. 104 is the deduced amino acid sequence of ESAT-6.
- SEQ. ID NO. 105 is the DNA sequence of TbH-8-2.
- SEQ. ID NO. 106 is the DNA sequence of TbH-9FL.
- 25 SEQ. ID NO. 107 is the deduced amino acid sequence of TbH-9FL.
- SEQ. ID NO. 108 is the DNA sequence of TbH-9-1.
- SEQ. ID NO. 109 is the deduced amino acid sequence of TbH-9-1.
- SEQ. ID NO. 110 is the DNA sequence of TbH-9-4.
- SEQ. ID NO. 111 is the deduced amino acid sequence of TbH-9-4.
- 30 SEQ. ID NO. 112 is the DNA sequence of Tb38-1F2 IN.

- SEQ. ID NO. 113 is the DNA sequence of Tb38-2F2 RP.
- SEQ. ID NO. 114 is the deduced amino acid sequence of Tb37-FL.
- SEQ. ID NO. 115 is the deduced amino acid sequence of Tb38-IN.
- SEQ. ID NO. 116 is the DNA sequence of Tb38-1F3.
- 5 SEQ. ID NO. 117 is the deduced amino acid sequence of Tb38-1F3.
- SEQ. ID NO. 118 is the DNA sequence of Tb38-1F5.
- SEQ. ID NO. 119 is the DNA sequence of Tb38-1F6.
- SEQ. ID NO. 120 is the deduced N-terminal amino acid sequence of DPV.
- SEQ. ID NO. 121 is the deduced N-terminal amino acid sequence of AVGS.
- 10 SEQ. ID NO. 122 is the deduced N-terminal amino acid sequence of AAMK.
- SEQ. ID NO. 123 is the deduced N-terminal amino acid sequence of YYWC.
- SEQ. ID NO. 124 is the deduced N-terminal amino acid sequence of DIGS.
- SEQ. ID NO. 125 is the deduced N-terminal amino acid sequence of AEES.
- SEQ. ID NO. 126 is the deduced N-terminal amino acid sequence of DPEP.
- 15 SEQ. ID NO. 127 is the deduced N-terminal amino acid sequence of APKT.
- SEQ. ID NO. 128 is the deduced amino acid sequence of DPAS.
- SEQ. ID NO. 129 is the protein sequence of DPPD N-terminal Antigen.
- SEQ ID NO. 130-133 are the protein sequences of four DPPD cyanogen bromide fragments.
- 20 SEQ ID NO. 134 is the N-terminal protein sequence of XDS antigen.
- SEQ ID NO. 135 is the N-terminal protein sequence of AGD antigen.
- SEQ ID NO. 136 is the N-terminal protein sequence of APE antigen.
- SEQ ID NO. 137 is the N-terminal protein sequence of XYI antigen.

25 Detailed Description of the Invention

As noted above, the present invention is generally directed to compositions and methods for preventing, treating and diagnosing tuberculosis. The compositions of the subject invention include polypeptides that comprise at least one immunogenic portion of a *M. tuberculosis* antigen, or a variant of such an antigen that 30 differs only in conservative substitutions and/or modifications. Polypeptides within the scope of the present invention include, but are not limited to, immunogenic soluble

M. tuberculosis antigens. A "soluble *M. tuberculosis* antigen" is a protein of *M. tuberculosis* origin that is present in *M. tuberculosis* culture filtrate. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins (*i.e.*, antigens), wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising an immunogenic portion of one of the above antigens may consist entirely of the immunogenic portion, or may contain additional sequences. The additional sequences may be derived from the native *M. tuberculosis* antigen or may be heterologous, and such sequences may (but need not) be immunogenic.

"Immunogenic," as used herein, refers to the ability to elicit an immune response (*e.g.*, cellular) in a patient, such as a human, and/or in a biological sample. In particular, antigens that are immunogenic (and immunogenic portions or other variants of such antigens) are capable of stimulating cell proliferation, interleukin-12 production and/or interferon- γ production in biological samples comprising one or more cells selected from the group of T cells, NK cells, B cells and macrophages, where the cells are derived from an *M. tuberculosis*-immune individual. Polypeptides comprising at least an immunogenic portion of one or more *M. tuberculosis* antigens may generally be used to detect tuberculosis or to induce protective immunity against tuberculosis in a patient.

The compositions and methods of this invention also encompass variants of the above polypeptides. A "variant," as used herein, is a polypeptide that differs from the native antigen only in conservative substitutions and/or modifications, such that the ability of the polypeptide to induce an immune response is retained. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the immunogenic properties of the modified polypeptide using, for example, the representative procedures described herein.

A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged. In general, the following

groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also (or alternatively) be modified by, for example, the
5 deletion or addition of amino acids that have minimal influence on the immunogenic properties, secondary structure and hydropathic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease
10 of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

In a related aspect, combination polypeptides are disclosed. A "combination polypeptide" is a polypeptide comprising at least one of the above
15 immunogenic portions and one or more additional immunogenic *M. tuberculosis* sequences, which are joined via a peptide linkage into a single amino acid chain. The sequences may be joined directly (i.e., with no intervening amino acids) or may be joined by way of a linker sequence (e.g., Gly-Cys-Gly) that does not significantly diminish the immunogenic properties of the component polypeptides.

20 In general, *M. tuberculosis* antigens, and DNA sequences encoding such antigens, may be prepared using any of a variety of procedures. For example, soluble antigens may be isolated from *M. tuberculosis* culture filtrate by procedures known to those of ordinary skill in the art, including anion-exchange and reverse phase chromatography. Purified antigens are then evaluated for their ability to elicit an
25 appropriate immune response (e.g., cellular) using, for example, the representative methods described herein. Immunogenic antigens may then be partially sequenced using techniques such as traditional Edman chemistry. See Edman and Berg, *Eur. J. Biochem.* 80:116-132, 1967.

Immunogenic antigens may also be produced recombinantly using a
30 DNA sequence that encodes the antigen, which has been inserted into an expression

- vector and expressed in an appropriate host. DNA molecules encoding soluble antigens may be isolated by screening an appropriate *M. tuberculosis* expression library with anti-sera (*e.g.*, rabbit) raised specifically against soluble *M. tuberculosis* antigens. DNA sequences encoding antigens that may or may not be soluble may be identified by
- 5 screening an appropriate *M. tuberculosis* genomic or cDNA expression library with sera obtained from patients infected with *M. tuberculosis*. Such screens may generally be performed using techniques well known to those of ordinary skill in the art, such as those described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989.
- 10 DNA sequences encoding soluble antigens may also be obtained by screening an appropriate *M. tuberculosis* cDNA or genomic DNA library for DNA sequences that hybridize to degenerate oligonucleotides derived from partial amino acid sequences of isolated soluble antigens. Degenerate oligonucleotide sequences for use in such a screen may be designed and synthesized, and the screen may be performed, as
- 15 described (for example) in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989 (and references cited therein). Polymerase chain reaction (PCR) may also be employed, using the above oligonucleotides in methods well known in the art, to isolate a nucleic acid probe from a cDNA or genomic library. The library screen may then be performed using the isolated
- 20 probe.

Alternatively, genomic or cDNA libraries derived from *M. tuberculosis* may be screened directly using peripheral blood mononuclear cells (PBMCs) or T cell lines or clones derived from one or more *M. tuberculosis*-immune individuals. In general, PBMCs and/or T cells for use in such screens may be prepared as described

25 below. Direct library screens may generally be performed by assaying pools of expressed recombinant proteins for the ability to induce proliferation and/or interferon- γ production in T cells derived from an *M. tuberculosis*-immune individual. Alternatively, potential T cell antigens may be first selected based on antibody reactivity, as described above.

Regardless of the method of preparation, the antigens (and immunogenic portions thereof) described herein (which may or may not be soluble) have the ability to induce an immunogenic response. More specifically, the antigens have the ability to induce proliferation and/or cytokine production (*i.e.*, interferon- γ and/or interleukin-12 production) in T cells, NK cells, B cells and/or macrophages derived from an *M. tuberculosis*-immune individual. The selection of cell type for use in evaluating an immunogenic response to a antigen will, of course, depend on the desired response. For example, interleukin-12 production is most readily evaluated using preparations containing B cells and/or macrophages. An *M. tuberculosis*-immune individual is one who is considered to be resistant to the development of tuberculosis by virtue of having mounted an effective T cell response to *M. tuberculosis* (*i.e.*, substantially free of disease symptoms). Such individuals may be identified based on a strongly positive (*i.e.*, greater than about 10 mm diameter induration) intradermal skin test response to tuberculosis proteins (PPD) and an absence of any signs or symptoms of tuberculosis disease. T cells, NK cells, B cells and macrophages derived from *M. tuberculosis*-immune individuals may be prepared using methods known to those of ordinary skill in the art. For example, a preparation of PBMCs (*i.e.*, peripheral blood mononuclear cells) may be employed without further separation of component cells. PBMCs may generally be prepared, for example, using density centrifugation through Ficoll™ (Winthrop Laboratories, NY). T cells for use in the assays described herein may also be purified directly from PBMCs. Alternatively, an enriched T cell line reactive against mycobacterial proteins, or T cell clones reactive to individual mycobacterial proteins, may be employed. Such T cell clones may be generated by, for example, culturing PBMCs from *M. tuberculosis*-immune individuals with mycobacterial proteins for a period of 2-4 weeks. This allows expansion of only the mycobacterial protein-specific T cells, resulting in a line composed solely of such cells. These cells may then be cloned and tested with individual proteins, using methods known to those of ordinary skill in the art, to more accurately define individual T cell specificity. In general, antigens that test positive in assays for proliferation and/or cytokine production (*i.e.*, interferon- γ and/or interleukin-12 production) performed using T cells, NK cells, B cells

and/or macrophages derived from an *M. tuberculosis*-immune individual are considered immunogenic. Such assays may be performed, for example, using the representative procedures described below. Immunogenic portions of such antigens may be identified using similar assays, and may be present within the polypeptides described herein.

- 5 The ability of a polypeptide (*e.g.*, an immunogenic antigen, or a portion or other variant thereof) to induce cell proliferation is evaluated by contacting the cells (*e.g.*, T cells and/or NK cells) with the polypeptide and measuring the proliferation of the cells. In general, the amount of polypeptide that is sufficient for evaluation of about 10^5 cells ranges from about 10 ng/mL to about 100 μ g/mL and preferably is about
10 10 μ g/mL. The incubation of polypeptide with cells is typically performed at 37°C for about six days. Following incubation with polypeptide, the cells are assayed for a proliferative response, which may be evaluated by methods known to those of ordinary skill in the art, such as exposing cells to a pulse of radiolabeled thymidine and measuring the incorporation of label into cellular DNA. In general, a polypeptide that
15 results in at least a three fold increase in proliferation above background (*i.e.*, the proliferation observed for cells cultured without polypeptide) is considered to be able to induce proliferation.

- 20 The ability of a polypeptide to stimulate the production of interferon- γ and/or interleukin-12 in cells may be evaluated by contacting the cells with the polypeptide and measuring the level of interferon- γ or interleukin-12 produced by the cells. In general, the amount of polypeptide that is sufficient for the evaluation of about 10^5 cells ranges from about 10 ng/mL to about 100 μ g/mL and preferably is about 10 μ g/mL. The polypeptide may, but need not, be immobilized on a solid support, such as a bead or a biodegradable microsphere, such as those described in U.S. Patent
25 Nos. 4,897,268 and 5,075,109. The incubation of polypeptide with the cells is typically performed at 37°C for about six days. Following incubation with polypeptide, the cells are assayed for interferon- γ and/or interleukin-12 (or one or more subunits thereof), which may be evaluated by methods known to those of ordinary skill in the art, such as an enzyme-linked immunosorbent assay (ELISA) or, in the case of IL-12 P70 subunit, a
30 bioassay such as an assay measuring proliferation of T cells. In general, a polypeptide

that results in the production of at least 50 pg of interferon- γ per mL of cultured supernatant (containing 10^4 - 10^5 T cells per mL) is considered able to stimulate the production of interferon- γ . A polypeptide that stimulates the production of at least 10 pg/mL of IL-12 P70 subunit, and/or at least 100 pg/mL of IL-12 P40 subunit, per 10^5 5 macrophages or B cells (or per 3×10^5 PBMC) is considered able to stimulate the production of IL-12.

In general, immunogenic antigens are those antigens that stimulate proliferation and/or cytokine production (*i.e.*, interferon- γ and/or interleukin-12 production) in T cells, NK cells, B cells and/or macrophages derived from at least about 10 25% of *M. tuberculosis*-immune individuals. Among these immunogenic antigens, polypeptides having superior therapeutic properties may be distinguished based on the magnitude of the responses in the above assays and based on the percentage of individuals for which a response is observed. In addition, antigens having superior therapeutic properties will not stimulate proliferation and/or cytokine production *in vitro* 15 in cells derived from more than about 25% of individuals that are not *M. tuberculosis*-immune, thereby eliminating responses that are not specifically due to *M. tuberculosis*-responsive cells. Those antigens that induce a response in a high percentage of T cell, NK cell, B cell and/or macrophage preparations from *M. tuberculosis*-immune individuals (with a low incidence of responses in cell 20 preparations from other individuals) have superior therapeutic properties.

Antigens with superior therapeutic properties may also be identified based on their ability to diminish the severity of *M. tuberculosis* infection in experimental animals, when administered as a vaccine. Suitable vaccine preparations for use on experimental animals are described in detail below. Efficacy may be 25 determined based on the ability of the antigen to provide at least about a 50% reduction in bacterial numbers and/or at least about a 40% decrease in mortality following experimental infection. Suitable experimental animals include mice, guinea pigs and primates.

Antigens having superior diagnostic properties may generally be 30 identified based on the ability to elicit a response in an intradermal skin test performed

on an individual with active tuberculosis, but not in a test performed on an individual who is not infected with *M. tuberculosis*. Skin tests may generally be performed as described below, with a response of at least 5 mm induration considered positive.

Immunogenic portions of the antigens described herein may be prepared 5 and identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3d ed., Raven Press, 1993, pp. 243-247 and references cited therein. Such techniques include screening polypeptide portions of the native antigen for immunogenic properties. The representative proliferation and cytokine production assays described herein may generally be employed in these screens. An immunogenic 10 portion of a polypeptide is a portion that, within such representative assays, generates an immune response (e.g., proliferation, interferon- γ production and/or interleukin-12 production) that is substantially similar to that generated by the full length antigen. In other words, an immunogenic portion of an antigen may generate at least about 20%, and preferably about 100%, of the proliferation induced by the full length antigen in the 15 model proliferation assay described herein. An immunogenic portion may also, or alternatively, stimulate the production of at least about 20%, and preferably about 100%, of the interferon- γ and/or interleukin-12 induced by the full length antigen in the model assay described herein.

Portions and other variants of *M. tuberculosis* antigens may be generated 20 by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are 25 sequentially added to a growing amino acid chain. See Merrifield, *J. Am. Chem. Soc.* 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Applied BioSystems, Inc., Foster City, CA, and may be operated according to the manufacturer's instructions. Variants of a native antigen may generally be prepared using standard mutagenesis techniques, such 30 as oligonucleotide-directed site-specific mutagenesis. Sections of the DNA sequence

may also be removed using standard techniques to permit preparation of truncated polypeptides.

Recombinant polypeptides containing portions and/or variants of a native antigen may be readily prepared from a DNA sequence encoding the polypeptide 5 using a variety of techniques well known to those of ordinary skill in the art. For example, supernatants from suitable host/vector systems which secrete recombinant protein into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or 10 more reverse phase HPLC steps can be employed to further purify a recombinant protein.

Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or 15 transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. The DNA sequences expressed in this manner may encode naturally occurring antigens, portions of naturally occurring antigens, or other 20 variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in substantially pure form. Preferably, the polypeptides are at least about 80% pure, more preferably at least about 90% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in 25 detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

In certain specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a soluble *M. tuberculosis* antigen having one of the following N-terminal sequences, or a variant thereof that 30 differs only in conservative substitutions and/or modifications:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 121)
- 5 (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 123)
- 10 (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val; (SEQ ID No. 124)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Ala-Ala-Ala-Ser-Pro-Pro-Ser; (SEQ ID No. 126)
- 15 (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly; (SEQ ID No. 127)
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128)
- 20 (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) or
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)
- 25

wherein Xaa may be any amino acid, preferably a cysteine residue. A DNA sequence encoding the antigen identified as (g) above is provided in SEQ ID No. 52, and the polypeptide encoded by SEQ ID No. 52 is provided in SEQ ID No. 53. A DNA sequence encoding the antigen defined as (a) above is provided in SEQ ID No. 101; its deduced amino acid sequence is provided in SEQ ID No. 102. A DNA sequence

corresponding to antigen (d) above is provided in SEQ ID No. 24 a DNA sequence corresponding to antigen (c) is provided in SEQ ID No. 25 and a DNA sequence corresponding to antigen (i) is provided in SEQ ID No. 99; its deduced amino acid sequence is provided in SEQ ID No. 100.

5 In a further specific embodiment, the subject invention discloses polypeptides comprising at least an immunogenic portion of an *M. tuberculosis* antigen having one of the following N-terminal sequences, or a variant thereof that differs only in conservative substitutions and/or modifications:

- 10 (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-
Ile-Asn-Val-His-Leu-Val; (SEQ ID No 137) or
(n) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-
Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129)

wherein Xaa may be any amino acid, preferably a cysteine residue.

15 In other specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a soluble *M. tuberculosis* antigen (or a variant of such an antigen) that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos.: 1, 2, 4-10, 13-25 and 52; (b) the complements of such DNA sequences, or (c) DNA sequences substantially homologous to a sequence in (a) or (b).

20 In further specific embodiments, the subject invention discloses polypeptides comprising at least an immunogenic portion of a *M. tuberculosis* antigen (or a variant of such an antigen), which may or may not be soluble, that comprises one or more of the amino acid sequences encoded by (a) the DNA sequences of SEQ ID Nos.: 26-51, (b) the complements of such DNA sequences or (c) DNA sequences substantially homologous to a sequence in (a) or (b).

25 In the specific embodiments discussed above, the *M. tuberculosis* antigens include variants that are encoded by DNA sequences which are substantially homologous to one or more of DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include

prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5X SSC, overnight or, in the case of cross-species homology at 45°C, 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS). Such hybridizing DNA sequences are also 5 within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of 10 the present invention and a known *M. tuberculosis* antigen, such as the 38 kD antigen described above or ESAT-6 (SEQ ID Nos. 103 and 104), together with variants of such fusion proteins. The fusion proteins of the present invention may also include a linker peptide between the first and second polypeptides.

A DNA sequence encoding a fusion protein of the present invention is 15 constructed using known recombinant DNA techniques to assemble separate DNA sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a DNA sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA 20 translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into 25 the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide 30 functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser

residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene* 40:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA* 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent 5 No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable 10 transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons require to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

15 In another aspect, the present invention provides methods for using one or more of the above polypeptides or fusion proteins (or DNA molecules encoding such polypeptides) to induce protective immunity against tuberculosis in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with a disease, or may be free of detectable disease and/or infection. In 20 other words, protective immunity may be induced to prevent or treat tuberculosis.

In this aspect, the polypeptide, fusion protein or DNA molecule is generally present within a pharmaceutical composition and/or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a 25 physiologically acceptable carrier. Vaccines may comprise one or more of the above polypeptides and a non-specific immune response enhancer, such as an adjuvant or a liposome (into which the polypeptide is incorporated). Such pharmaceutical compositions and vaccines may also contain other *M. tuberculosis* antigens, either incorporated into a combination polypeptide or present within a separate polypeptide.

Alternatively, a vaccine may contain DNA encoding one or more polypeptides as described above, such that the polypeptide is generated *in situ*. In such vaccines, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacterial and viral expression systems. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

In a related aspect, a DNA vaccine as described above may be administered simultaneously with or sequentially to either a polypeptide of the present invention or a known *M. tuberculosis* antigen, such as the 38 kD antigen described above. For example, administration of DNA encoding a polypeptide of the present invention, either "naked" or in a delivery system as described above, may be followed by administration of an antigen in order to enhance the protective immune effect of the vaccine.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunization using BCG. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Between 1 and 3 doses may be administered for a 1-36 week period. Preferably, 3 doses are administered, at

intervals of 3-4 months, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or DNA that, when administered as described above, is capable of raising an immune response in an immunized patient sufficient to protect the patient
5 from *M. tuberculosis* infection for at least 1-2 years. In general, the amount of polypeptide present in a dose (or produced *in situ* by the DNA in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 µg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

10 While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier,
15 such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic galactide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

20 Any of a variety of adjuvants may be employed in the vaccines of this invention to nonspecifically enhance the immune response. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune responses, such as lipid A, *Bordetella pertussis* or *Mycobacterium tuberculosis*. Suitable adjuvants are
25 commercially available as, for example, Freund's Incomplete Adjuvant and Freund's Complete Adjuvant (Difco Laboratories) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ). Other suitable adjuvants include alum, biodegradable microspheres, monophosphoryl lipid A and quil A.

30 In another aspect, this invention provides methods for using one or more of the polypeptides described above to diagnose tuberculosis using a skin test. As used

herein, a "skin test" is any assay performed directly on a patient in which a delayed-type hypersensitivity (DTH) reaction (such as swelling, reddening or dermatitis) is measured following intradermal injection of one or more polypeptides as described above. Such injection may be achieved using any suitable device sufficient to contact the 5 polypeptide or polypeptides with dermal cells of the patient, such as a tuberculin syringe or 1 mL syringe. Preferably, the reaction is measured at least 48 hours after injection, more preferably 48-72 hours.

The DTH reaction is a cell-mediated immune response, which is greater in patients that have been exposed previously to the test antigen (*i.e.*, the immunogenic 10 portion of the polypeptide employed, or a variant thereof). The response may be measured visually, using a ruler. In general, a response that is greater than about 0.5 cm in diameter, preferably greater than about 1.0 cm in diameter, is a positive response, indicative of tuberculosis infection, which may or may not be manifested as an active disease.

15 The polypeptides of this invention are preferably formulated, for use in a skin test, as pharmaceutical compositions containing a polypeptide and a physiologically acceptable carrier, as described above. Such compositions typically contain one or more of the above polypeptides in an amount ranging from about 1 μ g to about 100 μ g, preferably from about 10 μ g to about 50 μ g in a volume of 0.1 mL. 20 Preferably, the carrier employed in such pharmaceutical compositions is a saline solution with appropriate preservatives, such as phenol and/or Tween 80TM.

In a preferred embodiment, a polypeptide employed in a skin test is of sufficient size such that it remains at the site of injection for the duration of the reaction period. In general, a polypeptide that is at least 9 amino acids in length is sufficient. 25 The polypeptide is also preferably broken down by macrophages within hours of injection to allow presentation to T-cells. Such polypeptides may contain repeats of one or more of the above sequences and/or other immunogenic or nonimmunogenic sequences.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

5

EXAMPLE 1

PURIFICATION AND CHARACTERIZATION OF POLYPEPTIDES FROM *M. TUBERCULOSIS* CULTURE FILTRATE

10 This example illustrates the preparation of *M. tuberculosis* soluble polypeptides from culture filtrate. Unless otherwise noted, all percentages in the following example are weight per volume.

15 *M. tuberculosis* (either H37Ra, ATCC No. 25177, or H37Rv, ATCC No. 25618) was cultured in sterile GAS media at 37°C for fourteen days. The media was then vacuum filtered (leaving the bulk of the cells) through a 0.45 µ filter into a sterile 2.5 L bottle. The media was next filtered through a 0.2 µ filter into a sterile 4 L bottle and NaN₃ was added to the culture filtrate to a concentration of 0.04%. The bottles were then placed in a 4°C cold room.

20 The culture filtrate was concentrated by placing the filtrate in a 12 L reservoir that had been autoclaved and feeding the filtrate into a 400 ml Amicon stir cell which had been rinsed with ethanol and contained a 10,000 kDa MWCO membrane. The pressure was maintained at 60 psi using nitrogen gas. This procedure reduced the 12 L volume to approximately 50 ml.

25 The culture filtrate was dialyzed into 0.1% ammonium bicarbonate using a 8,000 kDa MWCO cellulose ester membrane, with two changes of ammonium bicarbonate solution. Protein concentration was then determined by a commercially available BCA assay (Pierce, Rockford, IL).

30 The dialyzed culture filtrate was then lyophilized, and the polypeptides resuspended in distilled water. The polypeptides were dialyzed against 0.01 mM 1,3 bis[tris(hydroxymethyl)-methylamino]propane, pH 7.5 (Bis-Tris propane buffer), the

initial conditions for anion exchange chromatography. Fractionation was performed using gel profusion chromatography on a POROS 146 II Q/M anion exchange column 4.6 mm x 100 mm (Perseptive BioSystems, Framingham, MA) equilibrated in 0.01 mM Bis-Tris propane buffer pH 7.5. Polypeptides were eluted with a linear 0-0.5 M NaCl gradient in the above buffer system. The column eluent was monitored at a wavelength of 220 nm.

The pools of polypeptides eluting from the ion exchange column were dialyzed against distilled water and lyophilized. The resulting material was dissolved in 0.1% trifluoroacetic acid (TFA) pH 1.9 in water, and the polypeptides were purified on 10 a Delta-Pak C18 column (Waters, Milford, MA) 300 Angstrom pore size, 5 micron particle size (3.9 x 150 mm). The polypeptides were eluted from the column with a linear gradient from 0-60% dilution buffer (0.1% TFA in acetonitrile). The flow rate was 0.75 ml/minute and the HPLC eluent was monitored at 214 nm. Fractions containing the eluted polypeptides were collected to maximize the purity of the 15 individual samples. Approximately 200 purified polypeptides were obtained.

The purified polypeptides were then screened for the ability to induce T-cell proliferation in PBMC preparations. The PBMCs from donors known to be PPD skin test positive and whose T-cells were shown to proliferate in response to PPD and crude soluble proteins from MTB were cultured in medium comprising RPMI 1640 20 supplemented with 10% pooled human serum and 50 µg/ml gentamicin. Purified polypeptides were added in duplicate at concentrations of 0.5 to 10 µg/mL. After six days of culture in 96-well round-bottom plates in a volume of 200 µl, 50 µl of medium was removed from each well for determination of IFN-γ levels, as described below. The plates were then pulsed with 1 µCi/well of tritiated thymidine for a further 18 25 hours, harvested and tritium uptake determined using a gas scintillation counter. Fractions that resulted in proliferation in both replicates three fold greater than the proliferation observed in cells cultured in medium alone were considered positive.

IFN-γ was measured using an enzyme-linked immunosorbent assay (ELISA). ELISA plates were coated with a mouse monoclonal antibody directed to 30 human IFN-γ (PharMingen, San Diego, CA) in PBS for four hours at room temperature.

Wells were then blocked with PBS containing 5% (W/V) non-fat dried milk for 1 hour at room temperature. The plates were then washed six times in PBS/0.2% TWEEN-20 and samples diluted 1:2 in culture medium in the ELISA plates were incubated overnight at room temperature. The plates were again washed and a polyclonal rabbit 5 anti-human IFN- γ serum diluted 1:3000 in PBS/10% normal goat serum was added to each well. The plates were then incubated for two hours at room temperature, washed and horseradish peroxidase-coupled anti-rabbit IgG (Sigma Chemical Co., St. Louis, MO) was added at a 1:2000 dilution in PBS/5% non-fat dried milk. After a further two hour incubation at room temperature, the plates were washed and TMB substrate added. 10 The reaction was stopped after 20 min with 1 N sulfuric acid. Optical density was determined at 450 nm using 570 nm as a reference wavelength. Fractions that resulted in both replicates giving an OD two fold greater than the mean OD from cells cultured in medium alone, plus 3 standard deviations, were considered positive.

For sequencing, the polypeptides were individually dried onto 15 BiobreneTM (Perkin Elmer/Applied BioSystems Division, Foster City, CA) treated glass fiber filters. The filters with polypeptide were loaded onto a Perkin Elmer/Applied BioSystems Division Procise 492 protein sequencer. The polypeptides were sequenced from the amino terminal and using traditional Edman chemistry. The amino acid sequence was determined for each polypeptide by comparing the retention time of the 20 PTH amino acid derivative to the appropriate PTH derivative standards.

Using the procedure described above, antigens having the following N-terminal sequences were isolated:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Xaa-Asn-Tyr-Gly-
Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 54)
- 25 (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-
Ser; (SEQ ID No. 55)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-
Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 56)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-
Pro; (SEQ ID No. 57)

- 5
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val;
(SEQ ID No. 58)
 - (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID
No. 59)
 - (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Ala-Ala-Ala-
Pro-Pro-Ala; (SEQ ID No. 60) and
 - (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-
Gly; (SEQ ID No. 61)

wherein Xaa may be any amino acid.

10 An additional antigen was isolated employing a microbore HPLC purification step in addition to the procedure described above. Specifically, 20 µl of a fraction comprising a mixture of antigens from the chromatographic purification step previously described, was purified on an Aquapore C18 column (Perkin Elmer/Applied Biosystems Division, Foster City, CA) with a 7 micron pore size, column size 1 mm x
15 100 mm, in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions were eluted from the column with a linear gradient of 1%/minute of acetonitrile (containing 0.05% TFA) in water (0.05% TFA) at a flow rate of 80 µl/minute. The eluent was monitored at 250 nm. The original fraction was separated into 4 major peaks plus other smaller components and a polypeptide was obtained which was shown to
20 have a molecular weight of 12.054 Kd (by mass spectrometry) and the following N-terminal sequence:

- 25
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Gln-
Thr-Ser-Leu-Leu-Asn-Asn-Leu-Ala-Asp-Pro-Asp-Val-Ser-Phe-
Ala-Asp (SEQ ID No. 62).

This polypeptide was shown to induce proliferation and IFN-γ production in PBMC preparations using the assays described above.

Additional soluble antigens were isolated from *M. tuberculosis* culture filtrate as follows. *M. tuberculosis* culture filtrate was prepared as described above. Following dialysis against Bis-Tris propane buffer, at pH 5.5, fractionation was
30 performed using anion exchange chromatography on a Poros QE column 4.6 x 100 mm

(Perseptive Biosystems) equilibrated in Bis-Tris propane buffer pH 5.5. Polypeptides were eluted with a linear 0-1.5 M NaCl gradient in the above buffer system at a flow rate of 10 ml/min. The column eluent was monitored at a wavelength of 214 nm.

The fractions eluting from the ion exchange column were pooled and 5 subjected to reverse phase chromatography using a Poros R2 column 4.6 x 100 mm (Perseptive Biosystems). Polypeptides were eluted from the column with a linear gradient from 0-100% acetonitrile (0.1% TFA) at a flow rate of 5 ml/min. The eluent was monitored at 214 nm.

Fractions containing the eluted polypeptides were lyophilized and 10 resuspended in 80 µl of aqueous 0.1% TFA and further subjected to reverse phase chromatography on a Vydac C4 column 4.6 x 150 mm (Western Analytical, Temecula, CA) with a linear gradient of 0-100% acetonitrile (0.1% TFA) at a flow rate of 2 ml/min. Eluent was monitored at 214 nm.

The fraction with biological activity was separated into one major peak 15 plus other smaller components. Western blot of this peak onto PVDF membrane revealed three major bands of molecular weights 14 Kd, 20 Kd and 26 Kd. These polypeptides were determined to have the following N-terminal sequences, respectively:

- (j) Xaa-Asp-Ser-Glu-Lys-Ser-Ala-Thr-Ile-Lys-Val-Thr-Asp-Ala-Ser; (SEQ ID No. 134)
- 20 (k) Ala-Gly-Asp-Thr-Xaa-Ile-Tyr-Ile-Val-Gly-Asn-Leu-Thr-Ala-Asp; (SEQ ID No. 135) and
- (l) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136), wherein Xaa may be any amino acid.

Using the assays described above, these polypeptides were shown to induce 25 proliferation and IFN- γ production in PBMC preparations. Figs. 1A and B show the results of such assays using PBMC preparations from a first and a second donor, respectively.

DNA sequences that encode the antigens designated as (a), (c), (d) and 30 (g) above were obtained by screening a genomic *M. tuberculosis* library using 32 P end labeled degenerate oligonucleotides corresponding to the N-terminal sequence and

containing *M. tuberculosis* codon bias. The screen performed using a probe corresponding to antigen (a) above identified a clone having the sequence provided in SEQ ID No. 101. The polypeptide encoded by SEQ ID No. 101 is provided in SEQ ID No. 102. The screen performed using a probe corresponding to antigen (g) above 5 identified a clone having the sequence provided in SEQ ID No. 52. The polypeptide encoded by SEQ ID No. 52 is provided in SEQ ID No. 53. The screen performed using a probe corresponding to antigen (d) above identified a clone having the sequence provided in SEQ ID No. 24, and the screen performed with a probe corresponding to antigen (c) identified a clone having the sequence provided in SEQ ID No. 25.

10 The above amino acid sequences were compared to known amino acid sequences in the gene bank using the DNA STAR system. The database searched contains some 173,000 proteins and is a combination of the Swiss, PIR databases along with translated protein sequences (Version 87). No significant homologies to the amino acid sequences for antigens (a)-(h) and (l) were detected.

15 The amino acid sequence for antigen (i) was found to be homologous to a sequence from *M. leprae*. The full length *M. leprae* sequence was amplified from genomic DNA using the sequence obtained from GENBANK. This sequence was then used to screen the *M. tuberculosis* library described below in Example 2 and a full length copy of the *M. tuberculosis* homologue was obtained (SEQ ID No. 99).

20 The amino acid sequence for antigen (j) was found to be homologous to a known *M. tuberculosis* protein translated from a DNA sequence. To the best of the inventors' knowledge, this protein has not been previously shown to possess T-cell stimulatory activity. The amino acid sequence for antigen (k) was found to be related to a sequence from *M. leprae*.

25 In the proliferation and IFN- γ assays described above, using three PPD positive donors, the results for representative antigens provided above are presented in Table 1:

TABLE 1
RESULTS OF PBMC PROLIFERATION AND IFN- γ ASSAYS

Sequence	Proliferation	IFN- γ
(a)	+	-
(c)	+++	+++
(d)	++	++
(g)	+++	+++
(h)	+++	+++

- 5 In Table 1, responses that gave a stimulation index (SI) of between 2 and 4 (compared to cells cultured in medium alone) were scored as +, an SI of 4-8 or 2-4 at a concentration of 1 μ g or less was scored as ++ and an SI of greater than 8 was scored as +++. The antigen of sequence (i) was found to have a high SI (+++) for one donor and lower SI (++) and (+) for the two other donors in both proliferation and IFN- γ assays.
- 10 These results indicate that these antigens are capable of inducing proliferation and/or interferon- γ production.

EXAMPLE 2
USE OF PATIENT SERA TO ISOLATE *M. TUBERCULOSIS* ANTIGENS

- 15 This example illustrates the isolation of antigens from *M. tuberculosis* lysate by screening with serum from *M. tuberculosis*-infected individuals.
- Dessicated *M. tuberculosis* H37Ra (Difco Laboratories) was added to a 2% NP40 solution, and alternately homogenized and sonicated three times. The resulting suspension was centrifuged at 13,000 rpm in microfuge tubes and the supernatant put through a 0.2 micron syringe filter. The filtrate was bound to Macro Prep DEAE beads (BioRad, Hercules, CA). The beads were extensively washed with 20 mM Tris pH 7.5 and bound proteins eluted with 1M NaCl. The 1M NaCl elute was dialyzed overnight against 10 mM Tris, pH 7.5. Dialyzed solution was treated with

DNase and RNase at 0.05 mg/ml for 30 min. at room temperature and then with α -D-mannosidase, 0.5 U/mg at pH 4.5 for 3-4 hours at room temperature. After returning to pH 7.5, the material was fractionated via FPLC over a Bio Scale-Q-20 column (BioRad). Fractions were combined into nine pools, concentrated in a Centriprep 10 5 (Amicon, Beverley, MA) and then screened by Western blot for serological activity using a serum pool from *M. tuberculosis*-infected patients which was not immunoreactive with other antigens of the present invention.

The most reactive fraction was run in SDS-PAGE and transferred to PVDF. A band at approximately 85 Kd was cut out yielding the sequence:

10 (m) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val: (SEQ ID No. 137), wherein Xaa may be any amino acid.

Comparison of this sequence with those in the gene bank as described above, revealed no significant homologies to known sequences.

15

EXAMPLE 3

PREPARATION OF DNA SEQUENCES ENCODING *M. TUBERCULOSIS* ANTIGENS

This example illustrates the preparation of DNA sequences encoding 20 *M. tuberculosis* antigens by screening a *M. tuberculosis* expression library with sera obtained from patients infected with *M. tuberculosis*, or with anti-sera raised against soluble *M. tuberculosis* antigens.

25 A. PREPARATION OF *M. TUBERCULOSIS* SOLUBLE ANTIGENS USING RABBIT ANTI-SERA

Genomic DNA was isolated from the *M. tuberculosis* strain H37Ra. The DNA was randomly sheared and used to construct an expression library using the Lambda ZAP expression system (Stratagene, La Jolla, CA). Rabbit anti-sera was generated against secretory proteins of the *M. tuberculosis* strains H37Ra, H37Rv and 30 Erdman by immunizing a rabbit with concentrated supernatant of the *M. tuberculosis* cultures. Specifically, the rabbit was first immunized subcutaneously with 200 μ g of

protein antigen in a total volume of 2 ml containing 10 µg muramyl dipeptide (Calbiochem, La Jolla, CA) and 1 ml of incomplete Freund's adjuvant. Four weeks later the rabbit was boosted subcutaneously with 100 µg antigen in incomplete Freund's adjuvant. Finally, the rabbit was immunized intravenously four weeks later with 50 µg protein antigen. The anti-sera were used to screen the expression library as described in 5 Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

10 Thirty two clones were purified. Of these, 25 represent sequences that have not been previously identified in human *M. tuberculosis*. Recombinant antigens were expressed and purified antigens used in the immunological analysis described in Example 1. Proteins were induced by IPTG and purified by gel elution, as described in Skeiky et al., *J. Exp. Med.* 181:1527-1537, 1995. Representative sequences of DNA 15 molecules identified in this screen are provided in SEQ ID Nos.: 1-25. The corresponding predicted amino acid sequences are shown in SEQ ID Nos. 63-87.

On comparison of these sequences with known sequences in the gene bank using the databases described above, it was found that the clones referred to hereinafter as TbRA2A, TbRA16, TbRA18, and TbRA29 (SEQ ID Nos. 76, 68, 70, 75) 20 show some homology to sequences previously identified in *Mycobacterium leprae* but not in *M. tuberculosis*. TbRA11, TbRA26, TbRA28 and TbDPEP (SEQ ID Nos.: 65, 73, 74, 53) have been previously identified in *M. tuberculosis*. No significant homologies were found to TbRA1, TbRA3, TbRA4, TbRA9, TbRA10, TbRA13, TbRA17, TbRa19, TbRA29, TbRA32, TbRA36 and the overlapping clones TbRA35 25 and TbRA12 (SEQ ID Nos. 63, 77, 81, 82, 64, 67, 69, 71, 75, 78, 80, 79, 66). The clone TbRa24 is overlapping with clone TbRa29.

The results of PBMC proliferation and interferon- γ assays performed on 30 representative recombinant antigens, and using T-cell preparations from several different *M. tuberculosis*-immune patients, are presented in Tables 2 and 3, respectively.

TABLE 2
RESULTS OF PBMC PROLIFERATION TO REPRESENTATIVE SOLUBLE ANTIGENS

Antigen	Patient												
	1	2	3	4	5	6	7	8	9	10	11	12	13
TbRa1	-	±	++	-	-	±	±	-	-	+	±	-	-
TbRa3	-	±	++	-	±	-	++	±	-	-	-	-	-
TbRa9	-	nt	nt	++	nt								
TbRa10	-	±	±	±	+	nt	±	-	+	±	±	±	-
TbRa11	±	±	+	++	+	nt	-	++	++	++	++	±	-
TbRa12	-	-	+	+	±	++	+	±	-	-	+	-	nt
TbRa16	nt	nt	nt	nt	-	+	nt	nt	nt	nt	nt	nt	-
TbRa24	nt	nt	nt	nt	-	-	nt						
TbRa26	-	+	nt	nt	-	-	nt						
TbRa29	nt	nt	nt	nt	-	-	nt						
TbRa35	++	nt	++	++	++	nt							
TbRaB	nt	nt	nt	nt	-	-	nt						
TbRaC	nt	nt	nt	nt	-	-	nt						
TbRaD	nt	nt	nt	nt	-	-	nt						
AAMK	-	-	±	-	-	-	nt	-	-	nt	±	±	-
YY	-	-	-	-	-	-	nt	-	-	nt	±	nt	-
DPEP	-	+	-	++	-	-	nt	-	-	nt	+	nt	-
Control	-	-	-	-	-	-	nt	++	±	+	±	nt	-

nt = not tested

TABLE 3
RESULTS OF PBM C INTERFERON- γ PRODUCTION TO REPRESENTATIVE SOLUBLE ANTIGENS

In Tables 2 and 3, responses that gave a stimulation index (SI) of between 1.2 and 2 (compared to cells cultured in medium alone) were scored as \pm , a SI of 2-4 was scored as +, as SI of 4-8 or 2-4 at a concentration of 1 μ g or less was scored as ++ and an SI of greater than 8 was scored as +++. In addition, the effect of 5 concentration on proliferation and interferon- γ production is shown for two of the above antigens in the attached Figure. For both proliferation and interferon- γ production, TbRa3 was scored as ++ and TbRa9 as +.

These results indicate that these soluble antigens can induce proliferation and/or interferon- γ production in T-cells derived from an *M. tuberculosis*-immune 10 individual.

B. USE OF PATIENT SERA TO IDENTIFY DNA SEQUENCES ENCODING M. TUBERCULOSIS ANTIGENS

The genomic DNA library described above, and an additional H37Rv 15 library, were screened using pools of sera obtained from patients with active tuberculosis. To prepare the H37Rv library, *M. tuberculosis* strain H37Rv genomic DNA was isolated, subjected to partial *Sau3A* digestion and used to construct an expression library using the Lambda Zap expression system (Stratagene, La Jolla, Ca). Three different pools of sera, each containing sera obtained from three individuals with 20 active pulmonary or pleural disease, were used in the expression screening. The pools were designated TbL, TbM and TbH, referring to relative reactivity with H37Ra lysate (*i.e.*, TbL = low reactivity, TbM = medium reactivity and TbH = high reactivity) in both ELISA and immunoblot format. A fourth pool of sera from seven patients with active pulmonary tuberculosis was also employed. All of the sera lacked increased reactivity 25 with the recombinant 38 kD *M. tuberculosis* H37Ra phosphate-binding protein.

All pools were pre-adsorbed with *E. coli* lysate and used to screen the H37Ra and H37Rv expression libraries, as described in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989. Bacteriophage plaques expressing immunoreactive antigens were purified. 30 Phagemid from the plaques was rescued and the nucleotide sequences of the *M. tuberculosis* clones deduced.

Thirty two clones were purified. Of these, 31 represented sequences that had not been previously identified in human *M. tuberculosis*. Representative sequences of the DNA molecules identified are provided in SEQ ID Nos.: 26-51 and 105. Of these, TbH-8 and TbH-8-2 (SEQ. ID NO. 105) are non-contiguous DNA sequences 5 from the same clone, and TbH-4 (SEQ. ID NO. 43) and TbH-4-FWD (SEQ. ID NO. 44) are non-contiguous sequences from the same clone. Amino acid sequences for the antigens hereinafter identified as Tb38-1, TbH-4, TbH-8, TbH-9, and TbH-12 are shown in SEQ ID Nos.: 88-92. Comparison of these sequences with known sequences 10 in the gene bank using the databases identified above revealed no significant homologies to TbH-4, TbH-8, TbH-9 and TbM-3, although weak homologies were found to TbH-9. TbH-12 was found to be homologous to a 34 kD antigenic protein 15 previously identified in *M. paratuberculosis* (Acc. No. S28515). Tb38-1 was found to be located 34 base pairs upstream of the open reading frame for the antigen ESAT-6 previously identified in *M. bovis* (Acc. No. U34848) and in *M. tuberculosis* (Sorensen et al., *Infec. Immun.* 63:1710-1717, 1995).

Probes derived from Tb38-1 and TbH-9, both isolated from an H37Ra library, were used to identify clones in an H37Rv library. Tb38-1 hybridized to Tb38-1F2, Tb38-1F3, Tb38-1F5 and Tb38-1F6 (SEQ. ID NOS. 112, 113, 116, 118, and 119). (SEQ ID NOS. 112 and 113 are non-contiguous sequences from clone Tb38-20 1F2.) Two open reading frames were deduced in Tb38-1F2; one corresponds to Tb37FL (SEQ. ID. NO. 114), the second, a partial sequence, may be the homologue of Tb38-1 and is called Tb38-IN (SEQ. ID NO. 115). The deduced amino acid sequence of Tb38-1F3 is presented in SEQ. ID. NO. 117. A TbH-9 probe identified three clones in the H37Rv library: TbH-9-FL (SEQ. ID NO. 106), which may be the homologue of TbH-9 25 (R37Ra), TbH-9-1 (SEQ. ID NO. 108), and TbH-9-4 (SEQ. ID NO. 110), all of which are highly related sequences to TbH-9. The deduced amino acid sequences for these three clones are presented in SEQ ID NOS. 107, 109 and 111.

The results of T-cell assays performed on Tb38-1, ESAT-6 and other 30 representative recombinant antigens are presented in Tables 4A, B and 5, respectively, below:

TABLE 4A
RESULTS OF PBMC PROLIFERATION TO REPRESENTATIVE ANTIGENS

Antigen	Donor										
	1	2	3	4	5	6	7	8	9	10	11
Tb38.1	+++	+	-	-	-	++	-	+	-	++	+++
ESAT-6	+++	+	+	+	-	+	-	+	+	++	+++
TbH-9	++	++	-	++	±	±	++	++	++	++	++

5

TABLE 4B
RESULTS OF PBMC INTERFERON-γ PRODUCTION TO REPRESENTATIVE ANTIGENS

Antigen	Donor										
	1	2	3	4	5	6	7	8	9	10	11
Tb38.1	+++	+	-	+	+	+++	-	++	-	+++	+++
ESAT-6	+++	+	+	+	+-	+	-	+	+	+++	+++
TbH-9	++	++	-	+++	±	±	+++	+++	++	+++	++

10

TABLE 5
SUMMARY OF T-CELL RESPONSES TO REPRESENTATIVE ANTIGENS

Antigen	Proliferation			Interferon- γ			total
	patient 4	patient 5	patient 6	patient 4	patient 5	patient 6	
TbH9	++	++	++	+++	++	++	13
TbM7	-	+	-	++	+	-	4
TbH5	-	+	+	++	++	++	8
TbL23	-	+	\pm	++	++	+	7.5
TbH4	-	++	\pm	++	++	\pm	7
- control	-	-	-	-	-	-	0

5

These results indicate that both the inventive *M. tuberculosis* antigens and ESAT-6 can induce proliferation and/or interferon- γ production in T-cells derived from an *M. tuberculosis*-immune individual. To the best of the inventors' knowledge, ESAT-6 has not been previously shown to stimulate human immune responses

10 A set of six overlapping peptides covering the amino acid sequence of the antigen Tb38-1 was constructed using the method described in Example 4. The sequences of these peptides, hereinafter referred to as pep1-6, are provided in SEQ ID Nos. 93-98, respectively. The results of T-cell assays using these peptides are shown in Tables 6 and 7. These results confirm the existence, and help to localize T-cell epitopes
15 within Tb38-1 capable of inducing proliferation and interferon- γ production in T-cells derived from an *M. tuberculosis* immune individual.

TABLE 6
RESULTS OF PBMC PROLIFERATION TO TB38-1 PEPTIDES

TABLE 7
RESULTS OF PBMC INTERFERON- γ PRODUCTION TO Tb38.1 PEPTIDES

EXAMPLE 4PURIFICATION AND CHARACTERIZATION OF A POLYPEPTIDE FROM TUBERCULIN PURIFIED PROTEIN DERIVATIVE

5

An *M. tuberculosis* polypeptide was isolated from tuberculin purified protein derivative (PPD) as follows.

PPD was prepared as published with some modification (Seibert, F. et al., Tuberculin purified protein derivative. Preparation and analyses of a large quantity 10 for standard. The American Review of Tuberculosis 44:9-25, 1941).

M. tuberculosis Rv strain was grown for 6 weeks in synthetic medium in roller bottles at 37°C. Bottles containing the bacterial growth were then heated to 100° C in water vapor for 3 hours. Cultures were sterile filtered using a 0.22 µ filter and the liquid phase was concentrated 20 times using a 3 kD cut-off membrane. Proteins were 15 precipitated once with 50% ammonium sulfate solution and eight times with 25% ammonium sulfate solution. The resulting proteins (PPD) were fractionated by reverse phase liquid chromatography (RP-HPLC) using a C18 column (7.8 x 300 mM; Waters, Milford, MA) in a Biocad HPLC system (Perseptive Biosystems, Framingham, MA). Fractions were eluted from the column with a linear gradient from 0-100% buffer (0.1% 20 TFA in acetonitrile). The flow rate was 10 ml/minute and eluent was monitored at 214 nm and 280 nm.

Six fractions were collected, dried, suspended in PBS and tested individually in *M. tuberculosis*-infected guinea pigs for induction of delayed type hypersensitivity (DTH) reaction. One fraction was found to induce a strong DTH 25 reaction and was subsequently fractionated further by RP-HPLC on a microbore Vydac C18 column (Cat. No. 218TP5115) in a Perkin Elmer/Applied Biosystems Division Model 172 HPLC. Fractions were eluted with a linear gradient from 5-100% buffer (0.05% TFA in acetonitrile) with a flow rate of 80 µl/minute. Eluent was monitored at 215 nm. Eight fractions were collected and tested for induction of DTH in *M. 30 tuberculosis*-infected guinea pigs. One fraction was found to induce strong DTH of

about 16 mm induration. The other fractions did not induce detectable DTH. The positive fraction was submitted to SDS-PAGE gel electrophoresis and found to contain a single protein band of approximately 12 kD molecular weight.

This polypeptide, herein after referred to as DPPD, was sequenced from 5 the amino terminal using a Perkin Elmer/Applied Biosystems Division Procise 492 protein sequencer as described above and found to have the N-terminal sequence shown in SEQ ID No.: 129. Comparison of this sequence with known sequences in the gene bank as described above revealed no known homologies. Four cyanogen bromide fragments of DPPD were isolated and found to have the sequences shown in SEQ ID 10 Nos.: 130-133.

The ability of the antigen DPPD to stimulate human PBMC to proliferate and to produce IFN- γ was assayed as described in Example 1. As shown in Table 8, DPPD was found to stimulate proliferation and elicit production of large quantities of IFN- γ ; more than that elicited by commercial PPD.

15

TABLE 8
RESULTS OF PROLIFERATION AND INTERFERON- γ ASSAYS TO DPPD

PBMC Donor	Stimulator	Proliferation (CPM)	IFN- γ (OD ₄₅₀)
A	Medium	1,089	0.17
	PPD (commercial)	8,394	1.29
	DPPD	13,451	2.21
B	Medium	450	0.09
	PPD (commercial)	3,929	1.26
	DPPD	6,184	1.49
C	Medium	541	0.11
	PPD (commercial)	8,907	0.76
	DPPD	23,024	>2.70

EXAMPLE 5SYNTHESIS OF SYNTHETIC POLYPEPTIDES

5

Polypeptides may be synthesized on a Millipore 9050 peptide synthesizer using Fmoc chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray mass spectrometry and by amino acid analysis.

20

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- (i) APPLICANTS: Corixa Corporation
- (ii) TITLE OF INVENTION: COMPOUNDS AND METHODS FOR IMMUNOTHERAPY AND DIAGNOSIS OF TUBERCULOSIS
- (iii) NUMBER OF SEQUENCES: 137
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: SEED and BERRY LLP
 - (B) STREET: 6300 Columbia Center, 701 Fifth Avenue
 - (C) CITY: Seattle
 - (D) STATE: Washington
 - (E) COUNTRY: USA
 - (F) ZIP: 98104-7092
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Floppy disk
 - (B) COMPUTER: IBM PC compatible
 - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 - (D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE: 27-AUG-1996
 - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Maki, David J.
 - (B) REGISTRATION NUMBER: 31,392
 - (C) REFERENCE/DOCKET NUMBER: 210121.411PC
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: (206) 622-4900
 - (B) TELEFAX: (206) 682-6031

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 766 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGAGGCACCG	GTAGTTGAA	CCAAACGCAC	AATCGACGGG	CAAACGAACG	GAAGAACACA	60
ACCATGAAGA	TGGTGAAATC	GATGCCGCA	GGTCTGACCG	CCGCGGCTGC	AATCGGGGCC	120
GCTGCGGCCG	GTGTGACTTC	GATCATGGCT	GGCGGCCCGG	TCGTATAACCA	GATGCAGCCG	180
GTCGTCTTCG	GCGCGCCACT	GCCGTTGGAC	CCGGCATCCG	CCCCTGACGT	CCCGACCGCC	240
GCCCAGTTGA	CCAGCCTGCT	CAACAGCCTC	GCCGATCCCA	ACGTGTCGTT	TGCGAACAAAG	300
GGCAGTCTGG	TCGAGGGCGG	CATCGGGGGC	ACCGAGGCGC	GCATCGCCGA	CCACAAGCTG	360
AAGAAGGCCG	CCGAGCACCG	GGATCTGGCG	CTGTCGTTCA	GCGTGACGAA	CATCCAGCCG	420
GCAGGCCCG	GTTCGGCCAC	CGCCGACGTT	TCCGTCTCGG	GTCCGAAGCT	CTCGTCGCCG	480
GTCACGCAGA	ACGTACGTT	CGTGAATCAA	GGCGGCTGGA	TGCTGTCACG	CGCATCGGCG	540
ATGGAGTTGC	TGCAGGCCGC	AGGGNAACTG	ATTGGCGGGC	CGGNTTCAGC	CCGCTGTTCA	600
GCTACGCCGC	CCGCCTGGTG	ACGCGTCCAT	GTCGAACACT	CGCGCGTGTA	GCACGGTGCG	660
GTNTGCGCAG	GGNCGCACGC	ACCGCCCGGT	GCAAGCCGTC	CTCGAGATAG	GTGGTGNCTC	720
GNCACCAGNG	ANCACCCCCN	NNTCGNCNNT	TCTCGNTGNT	GNATGA		766

(2) INFORMATION FOR SEQ ID NO:2:

- (A) LENGTH: 752 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

ATGCATCACCA ATCACCATCA CGATGAAGTC ACGGTAGAGA CGACCTCCGT CTTCCGCGCA	60
GACTTCCTCA GCGAGCTGGA CGCTCCTGCG CAAGCAGGGTA CGGAGAGCGC GGTCTCCGGG	120
GTGGAAGGGC TCCCGCCGGG CTCGGCGTTG CTGGTAGTCA AACGAGGCCA CAACGCCGGG	180
TCCCAGGTTCC TACTCGACCA AGCCATCACG TCGGCTGGTC GGCACTCCGA CAGCGACATA	240
TTTCTCGACG ACGTGACCGT GAGCCGTCGC CATGCTGAAT TCCGGTTGGA AAACAACGAA	300
TTCAATGTCG TCGATGTCGG GAGTCTAAC GGCACCTACG TCAACCGCGA GCCCGTGGAT	360
TCGGCGGTGC TGGCGAACGG CGACGAGGTC CAGATCGGCA AGCTCCGGTT GGTGTTCTTG	420
ACCGGACCCA AGCAAGGCGA GGATGACGGG AGTACCGGGG GCCCGTGAGC GCACCCGATA	480
GCCCCGCGCT GGCCGGGATG TCGATCGGGG CGGTCTCCG ACCTGCTACG ACCGGATTTT	540
CCCTGATGTC CACCATCTCC AAGATTGAT TCTTGGGAGG CTTGAGGGTC NGGGTGACCC	600
CCCCGCGGGC CTCATTCNGG GGTNTCGGCN GGTTTCACCC CNTACCNACT GCCNCCCGGN	660
TTGCNAATTG NTTCTTCNCT GCCCNAAAG GGACCNNTAN CTTGCCGCTN GAAANGGTNA	720
TCCNGGGCCC NTCTNGAAN CCCCNCCCC CT	752

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 813 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CATATGCATC ACCATCACCA TCACACTTCT AACCGCCAG CGCGTCGGGG GCGTCGAGCA	60
CCACCGCGACA CCGGGCCCGA TCGATCTGCT AGCTTGAGTC TGGTCAGGCA TCGTCGTAG	120
CAGCGCGATG CCCTATGTTT GTCGTCGACT CAGATATCGC GGCAATCCAA TCTCCCGCCT	180
GCGGCCGGCG GTGCTGCAA CTACTCCCGG AGGAATTTCG ACGTGCAT CAAGATCTTC	240
ATGCTGGTCA CGGCTGTCGT TTTGCTCTGT TGTTCGGGTG TGGCACGGC CGCGCCCAAG	300
ACCTACTGCG AGGAGTTGAA AGGCACCGAT ACCGGCCAGG CGTGCCAGAT TCAAATGTCC	360
GACCCGGCCT ACAACATCAA CATCAGCCTG CCCAGTTACT ACCCCGACCA GAAGTCGCTG	420
GAAAATTACA TCGCCCAGAC GCGCGACAAG TTCCCTCAGCG CGGCCACATC GTCCACTCCA	480
CGCGAAGCCC CCTACGAATT GAATATCACC TCGGCCACAT ACCAGTCCGC GATAACGCCG	540
CGTGGTACGC AGGCCGTGGT GCTCAMGGTC TACCACAACG CGGGCGGCAC GCACCCAAACG	600
ACCACGTACA AGGCCTTCGA TTGGGACCAAG GCCTATCGCA AGCCAATCAC CTATGACACG	660
CTGTGGCAGG CTGACACCGA TCCGCTGCCA GTCGTCTTCC CCATTGTTGC AAGGTGAAC	720
GAGCAACGCA GACCGGGACA ACWGGTATCG ATAGCCGCCN AATGCCGGCT TGGAACCCNG	780
TGAAATTATC ACAACTTCGC AGTCACNAAA NAA	813

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 447 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CGGTATGAAC ACGGCCGCGT CCGATAACTT CCAGCTGTCC CAGGGTGGGC AGGGATT CGC	60
CATTCCGATC GGGCAGGCGA TGGCGATCGC GGGCCAGATC CGATCGGTG GGGGGTCACC	120
CACCGTTCAT ATCGGGCCTA CCGCCTTCCT CGGCTTGGGT GTTGTGACA ACAACGGCAA	180
CGGCGCACGA GTCCAACGCG TGTCGGGAG CGCTCCGGCG GCAAGTCTCG GCATCTCCAC	240
CGGCGACGTG ATCACCGCGG TCGACGGCGC TCCGATCAAC TCGGCCACCG CGATGGCGGA	300
CGCGCTTAAC GGGCATCATC CCGGTGACGT CATCTCGGTG AACTGGCAA CCAAGTCGGG	360
CGGCACGCGT ACAGGGAACG TGACATTGGC CGAGGGACCC CGGGCCTGAT TTCGTCGYGG	420
ATACCACCCG CGGGCCGGCC AATTGGA	447

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 604 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GTCCCAC TGC GGTCGCCGAG TATGTCGCC CAGCAAATGTC TGGCAGCCGC CCAACGGAAT	60
CCGGTGATCC GACGTCGCAG GTTGTGAAAC CCGCCGCCGC GGAAGTATCG GTCCATGCCT	120
AGCCCCGGCGA CGGCGAGCGC CGGAATGGCG CGAGTGAGGA GGCAGGGCAAT TTGGCGGGGC	180
CCGGCGACGG NGAGCGCCGG AATGGCGCGA GTGAGGGAGGT GGNCAGTCAT GCCCAGNGTG	240
ATCCAATCAA CCTGNATTG GNCTGNGGN CCATTTGACA ATCGAGGTAG TGAGCGCAA	300
TGAATGATGG AAAACGGGNG GNGACGTCCG NTGTTCTGGT GGTGNTAGGT GNCTGNCTGG	360

NGTNGNGGNT ATCAGGATGT TCTTCGNCGA AANCTGATGN CGAGGAACAG GGTGTNCCCG	420
NNANNCCNAN GGNGTCCNAN CCCNNNNTCC TCGNCGANAT CANANAGNCG NTTGATGNGA	480
NAAAAGGGTG GANCAGNNNN AANTNGNGGN CCNAANAANC NNNANNGNNG NNAGNTNGNT	540
NNNTNTNNNC ANNNNNNNNTG NNGNNGNNCN NNNCAANCNN NTNNNNNGNAA NNGGNTTNTT	600
NAAT	604

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 633 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TTGCANGTCG AACCACCTCA CTAAAGGGAA CAAAAGCTNG AGCTCCACCG CGGTGGCGGC	60
CGCTCTAGAA CTAGTGKATM YYYCKGGCTG CAGSAATYCG GYACGAGCAT TAGGACAGTC	120
TAACGGTCCT GTTACGGTGA TCGAATGACC GACGACATCC TGCTGATCGA CACCGACGAA	180
CGGGTGCGAA CCCTCACCC CAACCGGCCG CAGTCCGYA ACGCGCTCTC GGCGGCGCTA	240
CGGGATCGGT TTTTCGCGGY GTTGGYCGAC GCCGAGGYCG ACGACGACAT CGACGTCGTC	300
ATCCTCACCG GYGCCGATCC GGTGTTCTGC GCCGGACTGG ACCTCAAGGT AGCTGGCCGG	360
GCAGACCGCG CTGCCGGACA TCTCACCGCG GTGGGCGGCC ATGACCAAGC CGGTGATCGG	420
CGCGATCAAC GGCGCCGCGG TCACCGCGG GCTCGAACTG GCGCTGTACT GCGACATCCT	480
GATCGCCTCC GAGCACGCC CTTCGNCGA CACCCACGCC CGGGTGGGGC TGCTGCCAC	540
CTGGGGACTC AGTGTGTGCT TGCCGAAAA GGTCGGCATC GGNCTGGGCC GGTGGATGAG	600
CCTGACCGGC GACTACCTGT CCGTGACCGA CGC	633

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1362 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CGACGACGAC	GGCGCCGGAG	AGCGGGCGCG	AACGGCGATC	GACGCCGGCCC	TGGCCAGAGT	60
CGGCACCACC	CAGGAGGGAG	TCGAATCATG	AAATTTGTCA	ACCATATTGA	GCCCCGTCGCG	120
CCCCGCCGAG	CCGGCGGCGC	GGTCGCCGAG	GTCTATGCCG	AGGCCCGCCG	CGAGTTCGGC	180
CGGCTGCCCG	AGCCGCTCGC	CATGCTGTCC	CCGGACGAGG	GACTGCTCAC	CGCCGGCTGG	240
GCGACGTTGC	GCGAGACACT	GCTGGTGGC	CAGGTGCCGC	GTGGCCGCAA	GGAAGCCGTC	300
GCCGCCGCCG	TCGGCGCCAG	CCTGCGCTGC	CCCTGGTGCG	TCGACGCACA	CACCACCATG	360
CTGTACGCGG	CAGGCCAAC	CGACACCGCC	GCGGCGATCT	TGGCCGGCAC	AGCACCTGCC	420
GCCGGTGACC	CGAACCGGCC	GTATGTGGCG	TGGGCGGCAG	GAACCGGGAC	ACCGGCGGGA	480
CCGCCGGCAC	CGTTCGGCC	GGATGTCGCC	GCCGAATACC	TGGGACCCGC	GGTGCATTG	540
CACTTCATCG	CACGCCCTGGT	CCTGGTGCTG	CTGGACGAAA	CCTTCCTGCC	GGGGGGCCCG	600
CGCGCCCAAC	AGCTCATGCG	CCGCGCCGGT	GGACTGGTGT	TCGCCCGCAA	GGTGCACGCG	660
GAGCATCGGC	CGGGCCGCTC	CACCCGCCGG	CTCGAGCCGC	GAACGCTGCC	CGACGATCTG	720
GCATGGGCAA	CACCGTCCGA	GCCCATAGCA	ACCGCGTTCG	CCGCGCTCAG	CCACCACCTG	780
GACACCGCGC	CGCACCTGCC	GCCACCGACT	CGTCAGGTGG	TCAGGCAGGT	CGTGGGGTCG	840
TGGCACGGCG	AGCCAATGCC	GATGAGCAGT	CGCTGGACGA	ACGAGCACAC	CGCCGAGCTG	900

CCCGCCGACC TGCACGCGCC CACCCGTCTT GCCCTGCTGA CGGGCCTGGC CCCGCATCAG	960
GTGACCGACG ACGACGTCGC CGCGGCCCGA TCCCTGCTCG ACACCGATGC GGCGCTGGTT	1020
GGCGCCCTGG CCTGGGCCGC CTTACCGCC GCGCGGCCGA TCGGCACCTG GATGGCGCC	1080
GCCGCCGAGG GCCAGGTGTC GCGGCAAAAC CCGACTGGGT GAGTGTGCGC GCCCTGTCGG	1140
TAGGGTGTCA TCGCTGGCCC GAGGGATCTC GCGGCGGCCGA ACGGAGGTGG CGACACAGGT	1200
GGAAGCTGCG CCCACTGGCT TGCGCCCCAA CGCCGTCGTG GGCGTTCGGT TGGCCGCACT	1260
GGCCGATCAG GTCGGCGCCG GCCCTGGCC GAAGGTCCAG CTAACGTGC CGTCACCGAA	1320
GGACCGGACG GTCACCGGGG GTCACCTGC GCGCCAAGG AA	1362

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1458 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GCGACGACCC CGATATGCCG GGCACCGTAG CGAAAGCCGT CGCCGACGCA CTCGGCGCG	60
GTATCGCTCC CGTTGAGGAC ATTCAAGGACT GCGTGGAGGC CGGGCTGGGG GAAGCCGGTC	120
TGGATGACGT GGCCCGTGT TACATCATCT ACCGGCAGCG GCGCGCCGAG CTGCGGACGG	180
CTAAGGCCTT GCTCGCGTG CGGGACGAGT TAAAGCTGAG CTTGGCGGCC GTGACGGTAC	240
TGCGCGAGCG CTATCTGCTG CACGACGAGC AGGGCCGGCC GGCCGAGTCG ACCGGCGAGC	300
TGATGGACCG ATCGGCGCGC TGTGTCGCGG CGGCCGAGGA CCAGTATGAG CCGGGCTCGT	360
CGAGGCGGTG GGCCGAGCGG TTGCCCCACGC TATTACGCAA CCTGGAATT CTGCCGAATT	420
CGCCCCACGTT GATGAACTCT GGCACCGACC TGGGACTGCT CGCCGGCTGT TTTGTTCTGC	480

CGATTGAGGA TTGCGCTGCAA TCGATCTTG CGACGCTGGG ACAGGCCGCC GAGCTGCAGC	540
GGGCTGGAGG CGGCACCGGA TATGCGTTCA GCCACCTGCG ACCCGCCGGG GATCGGGTGG	600
CCTCCACGGG CGGCACGGCC AGCGGACCGG TGTCGTTCT ACGGCTGTAT GACAGTGCCG	660
CGGGTGTGGT CTCCATGGGC GGTCGCCGGC GTGGCGCCTG TATGGCTGTG CTTGATGTGT	720
CGCACCCGGA TATCTGTGAT TTGTCACCG CCAAGGCCGA ATCCCCAGC GAGCTCCGC	780
ATTTAACCT ATCGGTTGGT GTGACCGACG CGTTCTGCG GGCGTCGAA CGAACCGGCC	840
TACACCGGCT GGTCAATCCG CGAACCGGCA AGATCGTCGC GCGGATGCCG GCCGCCGAGC	900
TGTTCGACGC CATCTGCAA GCCGCGCACG CCGGTGGCGA TCCCAGGCTG GTGTTCTCG	960
ACACGATCAA TAGGGCAAAC CCGGTGCCGG GGAGAGGCCG CATCGAGGCG ACCAACCCGT	1020
GCGGGGAGGT CCCACTGCTG CCTTACGAGT CATGTAATCT CGGCTCGATC AACCTGCC	1080
GGATGCTCGC CGACGGTCGC GTGACTGGG ACCGGCTCGA GGAGGTCGCC GGTGTGGCGG	1140
TGCGGTTCCCT TGATGACGTC ATCGATGTCA GCCGCTACCC CTTCCCCGAA CTGGGTGAGG	1200
CGGCCCCGCGC CACCCGCAAG ATCGGGCTGG GAGTCATGGG TTTGGCGGAA CTGCTTGCCG	1260
CACTGGGTAT TCCGTACGAC AGTGAAGAAG CCGTGCGGTT AGCCACCCGG CTCATGCGTC	1320
GCATACAGCA GGCGCGCAC ACGGCATCGC GGAGGCTGGC CGAAGAGCGG GGCGCATTC	1380
CGGCGTTCAC CGATAGCCGG TTCGCGCGGT CGGGCCCCGAG GCGCAACGCA CAGGTCACCT	1440
CCGTCGCTCC GACGGGCA	1458

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 862 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

ACGGTGTAAAT CGTGCTGGAT CTGGAACCGC GTGGCCCGCT ACCTACCGAG ATCTACTGGC 60
GGCGCAGGGG GCTGGCCCTG GGCATCGCGG TCGTCGTAGT CGGGATCGCG GTGGCCATCG 120
TCATCGCCTT CGTCGACAGC AGCGCCGGTG CCAAACCGGT CAGCGCCGAC AAGCCGGCCT 180
CCGCCAGAG CCATCCGGGC TCGCCGGCAC CCCAAGCACC CCAGCCGGCC GGGCAAACCG 240
AAGGTAACGC CGCCGCGGCC CCGCCGCAGG GCCAAAACCC CGAGACACCC ACGCCCACCG 300
CCGCGGTGCA GCCGCCGCCG GTGCTCAAGG AAGGGGACGA TTGCCCCGAT TCGACGCTGG 360
CCGTCAAAGG TTTGACCAAC GCGCCGCAGT ACTACGTGG CGACCAGCCG AAGTTCACCA 420
TGGTGGTCAC CAACATCGGC CTGGTGTCT GTAAACGCGA CGTTGGGCC GCGGTGTTGG 480
CCGCCTACGT TTACTCGCTG GACAACAAGC GGTTGTGGTC CAACCTGGAC TGCGCCGCC 540
CGAATGAGAC GCTGGTCAAG ACGTTTCCC CCGGTGAGCA GGTAACGACC GCGGTGACCT 600
GGACCGGGAT GGGATCGGCG CCGCGCTGCC CATTGCCGCG GCCGGCGATC GGGCCGGGCA 660
CCTACAATCT CGTGGTACAA CTGGCAATC TGCGCTCGCT GCCGGTTCCG TTCATCCTGA 720
ATCAGCCGCC GCCGCCGCC GGGCCGGTAC CCGCTCCGGG TCCAGCGCAG GCGCCTCCGC 780
CGGAGTCTCC CGCGCAAGGC GGATAATTAT TGATCGCTGA TGGTCGATTC CGCCAGCTGT 840
GACAACCCCT CGCCTCGTGC CG 862

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 622 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTGATCAGCA CCGGCAAGGC GTCACATGCC TCCCTGGGTG TGCAAGGTGAC CAATGACAAA	60
GACACCCCGG GCGCCAAGAT CGTCGAAGTA GTGGCCGGTG GTGCTGCCGC GAACGCTGGA	120
GTGCCGAAGG GCGTCGTTGT CACCAAGGTC GACGACCGCC CGATCAACAG CGCGGACGCG	180
TTGGTTGCCG CCGTGCACGG CAAAGCGCCG GGCGCCACGG TGGCGCTAAC CTTTCAGGAT	240
CCCTCGGGCG GTAGCCGCAC AGTGCAAGTC ACCCTCGGCA AGGCGGAGCA GTGATGAAGG	300
TCGCCGCGCA GTGTTCAAAG CTCGGATATA CGGTGGCACC CATGGAACAG CGTGCAGGAGT	360
TGGTGGTTGG CCGGGCACTT GTCGTCGTCG TTGACGATCG CACGGCGCAC GGCGATGAAG	420
ACCACAGCGG GCCGCTTGTC ACCGAGCTGC TCACCGAGGC CGGGTTTGTT GTCGACGGCG	480
TGGTGGCGGT GTCGGCCGAC GAGGTCGAGA TCCGAAATGC GCTGAACACA GCGGTGATCG	540
GCGGGGTGGA CCTGGTGGTG TCGGTCGGCG GGACCGGNGT GACGNCTCGC GATGTCACCC	600
CGGAAGCCAC CCGNGACATT CT	622

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1200 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGCGCAGCGG TAAGCCTGTT GGCCGCCGGC ACACTGGGTG TGACAGCATG CGGCAGGTGGC	60
ACCAACAGCT CGTCGTCAGG CGCAGGCGGA ACGTCTGGGT CGGTGCAGTG CGGCAGGCAAG	120
AAGGAGCTCC ACTCCAGCGG CTCGACCGCA CAAGAAAATG CCATGGAGCA GTTCGTCTAT	180

GCCTACGTGC GATCGTGCCC	GGGCTACACG TTGGACTACA	ACGCCAACGG GTCCGGTGCC	240
GGGGTGACCC AGTTTCTCAA	CAACGAAACC GATTTCGCCG	GCTCGGATGT CCCGTTGAAT	300
CCGTCGACCG GTCAACCTGA	CCGGTCGGCG GAGCGGTGCG	GTTCCCCGGC ATGGGACCTG	360
CCGACGGTGT TCGGCCCCAT	CGCGATCACCC TACAATATCA	AGGGCGTGAG CACGCTGAAT	420
CTTGACGGAC CCACTACCGC	CAAGATTTTC AACGGCACCA	TCACCGTGTG GAATGATCCA	480
CAGATCCAAG CCCTCAACTC	CGGCACCGAC CTGCCGCCAA	CACCGATTAG CGTTATCTTC	540
CGCAGCGACA AGTCCGGTAC	GTCGGACAAC TTCCAGAAAT	ACCTCGACGG TGTATCCAAC	600
GGGGCGTGGG GCAAAGGCAC	CAGCGAAACG TTCAGCGGGG	CGCTCGGCGT CGGCGCCAGC	660
GGGAACAAACG GAACGTCGGC	CCTACTGCAG ACGACCGACG	GGTCGATCAC CTACAACGAG	720
TGGTCGTTTG CGGTGGGTAA	GCAGTTGAAC ATGGCCCAGA	TCATCACGTC GGCGGGTCCG	780
GATCCAGTGG CGATCACCAC	CGAGTCGGTC GGTAAAGACAA	TCGCCGGGGC CAAGATCATG	840
GGACAAGGCA ACGACCTGGT	ATTGGACACG TCGTCGTTCT	ACAGACCCAC CCAGCCTGGC	900
TCTTACCGA TCGTGCTGGC	GACCTATGAG ATCGTCTGCT	CGAAATAACC GGATGCGACG	960
ACCGGTACTG CGGTAAGGGC	GTTTATGCAA GCCGCGATTG	GTCCAGGCCA AGAAGGCCTG	1020
GACCAATACG GCTCCATTCC	GTTGCCAAA TCGTTCCAAG	CAAATTGGC GGCCGCGGTG	1080
AATGCTATTT CTTGACCTAG	TGAAGGGAAT TCGACGGTGA	GCGATGCCGT TCCGCAGGTA	1140
GGGTCGCAAT TTGGGCCGTA	TCAGCTATTG CGGCTGCTGG	GCCGAGGCAG GATGGGCGAG	1200

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1155 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GCAAGCAGCT	GCAGGGTCGTG	CTGTTCGACG	AACTGGGCAT	GCCGAAGACC	AAACGCACCA	60
AGACCGGGCTA	CACCACGGAT	GCCGACGCGC	TGCAGTCGTT	GTTCGACAAG	ACCGGGCATC	120
CGTTTCTGCA	ACATCTGCTC	GCCCACCGCG	ACGTCACCCG	GCTCAAGGTC	ACCGTCGACG	180
GGTTGCTCCA	AGCGGTGGCC	GCCGACGGCC	GCATCCACAC	CACGTTCAAC	CAGACGATCG	240
CCGCGACCGG	CCGGCTCTCC	TCGACCGAAC	CCAACCTGCA	GAACATCCCG	ATCCGCACCG	300
ACGCGGGCCG	GCGGATCCGG	GACGCGTTCG	TGGTCGGGGA	CGGTTACGCC	GAGTTGATGA	360
CGGCCGACTA	CAGCCAGATC	GAGATGCGGA	TCATGGGGCA	CCTGTCCGGG	GACGAGGGCC	420
TCATCGAGGC	GTTCAACACC	GGGGAGGGACC	TGTATTGTT	CGTCGCGTCC	CGGGTGTTCG	480
GTGTGCCCAT	CGACGAGGTC	ACCGGCGAGT	TGCGGCGCCG	GGTCAAGGCG	ATGTCCTACG	540
GGCTGGTTTA	CGGGTTGAGC	GCCTACGGCC	TGTCGCAGCA	GTTGAAAATC	TCCACCGAGG	600
AAGCCAACGA	GCAGATGGAC	GCGTATTCG	CCCGATTCTGG	CGGGGTGCGC	GACTACCTGC	660
GCGCCGTAGT	CGAGCGGGCC	CGCAAGGACG	GCTACACCTC	GACGGTGCTG	GGCCGTCGCC	720
GCTACCTGCC	CGAGCTGGAC	AGCAGCAACC	GTCAAGTGCG	GGAGGCCGCC	GAGCGGGCGG	780
CGCTGAACGC	GCCGATCCAG	GGCAGCGCGG	CCGACATCAT	CAAGGTGGCC	ATGATCCAGG	840
TCGACAAGGC	GCTCAACGAG	GCACAGCTGG	CGTCGCGCAT	GCTGCTGCAG	GTCCACGACG	900
AGCTGCTGTT	CGAAATCGCC	CCCGGTGAAC	GCGAGCGGGT	CGAGGCCCTG	GTGCGCGACA	960
AGATGGGCGG	CGCTTACCCG	CTCGACGTCC	CGCTGGAGGT	GTCGGTGGC	TACGGCCGCA	1020
GCTGGGACGC	GGCGGCGCAC	TGAGTGCCGA	GCGTGCATCT	GGGGCGGGAA	TTCGGCGATT	1080
TTTCCGCCCT	GAGTTCACGC	TCGGCGCAAT	CGGGACCGAG	TTTGTCCAGC	GTGTACCCGT	1140
CGAGTAGCCT	CGTCA					1155

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1771 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GAGCGCCGTC	TGGTGTTTGA	ACGGTTTAC	CGGTGGCAT	CGGCACGGGC	GTTGCCGGT	60
TCGGGCCTCG	GGTTGGCGAT	CGTAAACAG	GTGGTGCTCA	ACCACGGCGG	ATTGCTGCGC	120
ATCGAAGACA	CCGACCCAGG	CGGCCAGCCC	CCTGGAACGT	CGATTACGT	GCTGCTCCCC	180
GGCCGTCGGA	TGCCGATTCC	GCAGCTTCCC	GGTGCACGG	CTGGCGCTCG	GAGCACGGAC	240
ATCGAGAACT	CTCGGGGTTC	GGCGAACGTT	ATCTCAGTGG	AATCTCAGTC	CACGCGCGCA	300
ACCTAGTTGT	GCAGTTACTG	TTGAAAGCCA	CACCCATGCC	AGTCACGCA	TGGCCAAGTT	360
GGCCCGAGTA	GTGGGCCTAG	TACAGGAAGA	GCAACCTAGC	GACATGACGA	ATCACCCACG	420
GTATTGCCA	CCGCCGCAGC	AGCCGGGAAC	CCCAGGTTAT	GCTCAGGGGC	AGCAGCAAAC	480
GTACAGCCAG	CAGTCGACT	GGCGTTACCC	ACCGTCCCCG	CCCCCGCAGC	CAACCCAGTA	540
CCGTCAACCC	TACGAGGCCT	TGGGTGGTAC	CCGGCCGGGT	CTGATACCTG	GCGTGATTCC	600
GACCATGACG	CCCCCTCCTG	GGATGGTTCG	CCAACGCCCT	CGTGCAGGCA	TGTTGGCCAT	660
CGGCGCGGTG	ACGATAGCGG	TGGTGTCGC	CGGCATCGGC	GGCGCGGCCG	CATCCCTGGT	720
CGGGTTCAAC	CGGGCACCCG	CGGGCCCCAG	CGGCAGGCCA	GTGGCTGCCA	GCGCGCGGCC	780
AAGCATCCCC	GCAGCAAACA	TGCCGCCGGG	GTCGGTCGAA	CAGGTGGCGG	CCAAGGTGGT	840
GCCCAGTGTC	GTCATGTTGG	AAACCGATCT	GGGCCGCCAG	TCGGAGGAGG	GCTCCGGCAT	900
CATTCTGTCT	GCCGAGGGGC	TGATCTTGAC	CAACAACCAC	GTGATCGCGG	CGGCCGCCAA	960

60

GCCTCCCCTG	GGCAGTCCGC	CGCCGAAAAC	GACGGTAACC	TTCTCTGACG	GGCGGACCGC	1020
ACCCTTCACG	GTGGTGGGGG	CTGACCCCAC	CAGTGATATC	GCCGTCGTCC	GTGTTCAGGG	1080
CGTCTCCGGG	CTCACCCCCA	TCTCCCTGGG	TTCCCTCTCG	GACCTGAGGG	TCGGTCAGCC	1140
GGTGCTGGCG	ATCGGGTCGC	CGCTCGGTTT	GGAGGGCACC	GTGACCACGG	GGATCGTCAG	1200
CGCTCTCAAC	CGTCCAGTGT	CGACGACCGG	CGAGGCCGGC	AACCAGAACAA	CCGTGCTGGA	1260
CGCCATTCA	ACCGACGCCG	CGATCAACCC	CGGTAACTCC	GGGGGCGCGC	TGGTGAACAT	1320
GAACGCTCAA	CTCGTCGGAG	TCAACTCGGC	CATTGCCACG	CTGGGCGCGG	ACTCAGCCGA	1380
TGCGCAGAGC	GGCTCGATCG	GTCTCGGTTT	TGCGATTCCA	GTCGACCAGG	CCAAGCGCAT	1440
CGCCGACGAG	TTGATCAGCA	CCGGCAAGGC	GTCACATGCC	TCCCTGGGTG	TGCAGGTGAC	1500
CAATGACAAA	GACACCCCGG	GCGCCAAGAT	CGTCGAAGTA	GTGGCCGGTG	GTGCTGCCGC	1560
GAACGCTGGA	GTGCCGAAGG	GCGTCGTTGT	CACCAAGGTC	GACGACCGCC	CGATCAACAG	1620
CGCGGACGCG	TTGGTTGCCG	CCGTGCGGTC	CAAAGCGCCG	GGCGCCACGG	TGGCGCTAAC	1680
CTTCAGGAT	CCCTCGGGCG	GTAGCCGCAC	AGTGCAAGTC	ACCCTCGGCA	AGGCGGAGCA	1740
GTGATGAAGG	TCGCCCGC	GTGTTCAAAG	C			1771

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1058 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTCCACCGCG	GTGGCGGCCG	CTCTAGAACT	AGTGGATCCC	CCGGGCTGCA	GGAATT CGGC	60
ACGAGGATCC	GACGTCGCAG	GTTGTCGAAC	CCGCCGCCGC	GGAAGTATCG	GTCCATGCCT	120

AGCCCGGCGA CGCGGAGCGC CGGAATGGCG CGAGTGAGGA GGCAGGCAAT TTGGCGGGGC	180
CCGGCGACGG CGAGCGCCGG AATGGCGCGA GTGAGGAGGC GGGCAGTCAT GCCCAGCGTG	240
ATCCAATCAA CCTGCATTG GCCTGCGGGC CCATTTGACA ATCGAGGTAG TGAGCGCAAA	300
TGAATGATGG AAAACGGGCG GTGACGTCCG CTGTTCTGGT GGTGCTAGGT GCCTGCCCTGG	360
CGTTGTGGCT ATCAGGATGT TCTTCGCCGA AACCTGATGC CGAGGAACAG GGTGTTCCCG	420
TGAGCCCGAC GGCGTCCGAC CCCCGCCTCC TCGCCGAGAT CAGGCAGTCG CTTGATGCGA	480
CAAAAGGGTT GACCAGCGTG CACGTAGCGG TCCGAACAAC CGGGAAAGTC GACAGCTTGC	540
TGGGTATTAC CAGTGCCGAT GTCGACGTCC GGGCCAATCC GCTCGCGCA AAGGGCGTAT	600
GCACCTACAA CGACGAGCAG GGTGTCCCGT TTCGGGTACA AGGCAGACAAC ATCTCGGTGA	660
AACTGTTCGA CGACTGGAGC AATCTGGCT CGATTTCTGA ACTGTCAACT TCACGCGTGC	720
TCGATCCTGC CGCTGGGTG ACGCAGCTGC TGTCCGGTGT CACGAACCTC CAAGCGCAAG	780
GTACCGAAGT GATAGACGGA ATTCGACCA CCAAAATCAC CGGGACCATC CCCGCGAGCT	840
CTGTCAAGAT GCTTGATCCT GGCGCCAAGA GTGCAAGGCC GGCGACCGTG TGGATTGCC	900
AGGACGGCTC GCACCACCTC GTCCGAGCGA GCATCGACCT CGGATCCGGG TCGATTCA	960
TCACGCAGTC GAAATGGAAC GAACCCGTCA ACGTCGACTA GGCCGAAGTT GCGTCGACGC	1020
GTTGNTCGAA ACGCCCTTGT GAACGGTGTC AACGGNAC	1058

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 542 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GAATTGGCA CGAGAGGTGA TCGACATCAT CGGGACCAGC CCCACATCCT GGGAACAGGC	60
GGCGGCGGAG GCGGTCCAGC GGGCGCGGA TAGCGTCGAT GACATCCGCG TCGCTCGGGT	120
CATTGAGCAG GACATGGCCG TGGACAGCGC CGGCAAGATC ACCTACCGCA TCAAGCTCGA	180
AGTGTGTT AAGATGAGGC CGGCGCAACC GCGCTAGCAC GGGCCGGCGA GCAAGACGCA	240
AAATCGCACG GTTGGCGTT GATTGCGCG ATTGTCGTC TGCTGCCGA GGCCTACCAAG	300
GCGCGGCCA GGTCCGCGTG CTGCCGTATC CAGGCGTGCA TCGCGATTCC GGCGGCCACG	360
CCGGAGTTAA TGCTTCGCGT CGACCCGAAC TGGGCGATCC GCCGGNGAGC TGATCGATGA	420
CCGTGGCCAG CCCGTCGATG CCCGAGTTGC CCGAGGAAAC GTGCTGCCAG GCCGGTAGGA	480
AGCGTCCGTA GGCGGCGGTG CTGACCGGCT CTGCCTGCGC CCTCAGTGC GCGAGCGAGC	540
GG	542

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 913 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CGGTGCCGCC CGCGCCTCCG TTGCCCAT TGCCGCCGTC GCCGATCAGC TGCGCATCGC	60
CACCATCACC GCCTTGCCG CCGGCACCGC CGGTGGCGCC GGGGCCGCG ATGCCACCGC	120
TTGACCTGG CCGCCGGCGC CGCCATTGCC ATACAGCACC CCGCCGGGG CACCGTTACC	180
GCCGTCGCCA CCGTCGCCGC CGCTGCCGTT TCAGGCCGGG GAGGCCGAAT GAACCGCCGC	240
CAAGCCGCC GCCGGCACCG TTGCCGCCTT TTCCGCCGC CCCGCCGGCG CCGCCAATTG	300

CCGAACAGCC AMGCACCGTT GCCGCCAGCC CCGCCGCCGT TAACGGCGCT GCCGGGCGCC	360
GCCGCCGGAC CCGCCATTAC CGCCGTTCCC GTTCGGTGCC CCGCCGTTAC CGGCGCCGCC	420
GTTCGCCGCC AATATTCGGC GGGCACCGCC AGACCCGCCG GGGCCACCAT TGCCGCCGGG	480
CACCGAAACA ACAGCCCAAC GGTGCCGCCG GCCCGCCGT TTGCCGCCAT CACCGGCCAT	540
TCACCGCCAG CACCGCCGTT AATGTTTATG AACCCGGTAC CGCCAGCGCG GCCCCTATTG	600
CCGGGCCGCCG GAGNGCGTGC CCGCCGCCGC CGCCAACGCC CAAAAGCCCG GGGTTGCCAC	660
CGGCCCCGCC GGACCCACCG GTCCCGCCGA TCCCCCGTT GCCGCCGGTG CCGCCGCCAT	720
TGGTGCTGCT GAAGCCGTTA GCGCCGGTTC CGCSGGTTCC GGCGGTGGCG CCNTGGCCGC	780
CGGCCCCGCC GTTGCCGTAC AGCCACCCCC CGGTGGCGCC GTTGCCGCCA TTGCCGCCAT	840
TGCCGCCGTT GCCGCCATTG CCGCCGTTCC CGCCGCCACC GCCGGNTTGG CCGCCGGCGC	900
CGCCGGCGGC CGC	913

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1872 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GAATACGTTG GTGTAGAAAA ATCCTGCCGC CCGGACCCCTT AAGGCTGGGA CAATTTCTGA	60
TAGCTACCCC GACACAGGAG GTTACGGGAT GAGCAATTG CGCCGCCGCT CACTCAGGTG	120
GTCATGGTTG CTGAGCGTGC TGGCTGCCGT CGGGCTGGGC CTGGCCACGG CGCCGGCCCA	180
GGCGGGCCCCG CGGGCCTTGT CGCAGGACCG GTTCGCCGAC TTCCCCGCCGC TGCCCCCTCGA	240

CCCGTCCGCG	ATGGTCGCC	AAGTGGGCC	ACAGGTGGTC	AACATCAACA	CCAAACTGGG	300
CTACAACAAAC	GCCGTGGCG	CCGGGACCGG	CATCGTCATC	GATCCAACG	GTGTCGTGCT	360
GACCAACAAAC	CACGTGATCG	CGGGCGCCAC	CGACATCAAT	GCGTTCAGCG	TCGGCTCCGG	420
CCAAACCTAC	GGCGTCGATG	TGGTCGGTA	TGACCGCACC	CAGGATGTCG	CGGTGCTGCA	480
GCTGCGCGGT	GCCGGTGGCC	TGCCGTGGC	GGCGATCGGT	GGCGGCGTCG	CGGTTGGTGA	540
GCCC GTCGTC	GCGATGGGCA	ACAGCGGTGG	GCAGGGCGGA	ACGCCCCGTG	CGGTGCCTGG	600
CAGGGTGGTC	GCGCTCGGCC	AAACCGTGCA	GGCGTCGGAT	TCGCTGACCG	GTGCCGAAGA	660
GACATTGAAC	GGGTTGATCC	AGTCGATGC	CGCAATCCAG	CCCGGTGATT	CGGGCGGGCC	720
CGTCGTCAAC	GGCCTAGGAC	AGGTGGTCGG	TATGAACACG	GCCGCGTCCG	ATAACTTCCA	780
GCTGTCCCAG	GGTGGGCAGG	GATTGCCAT	TCCGATCGGG	CAGGCGATGG	CGATCGCGGG	840
CCAAATCCGA	TCGGGTGGGG	GGTCACCCAC	CGTTCATATC	GGGCCTACCG	CCTTCCTCGG	900
CTTGGGTGTT	GTCGACAACA	ACGGCAACGG	CGCACGAGTC	CAACGCGTGG	TCGGAAGCGC	960
TCCGGCGGCA	AGTCTCGGCA	TCTCCACCGG	CGACGTGATC	ACCGCGGTG	ACGGCGCTCC	1020
GATCAA CTG	GCCACCGCGA	TGGCGGACGC	GCTTAACGGG	CATCATCCCG	GTGACGTCAT	1080
CTCGGTGAAC	TGGCAAACCA	AGTCGGCGG	CACGCGTACA	GGGAACGTGA	CATTGGCGA	1140
GGGACCCCCG	GCCTGATTTG	TCGCGGATAC	CACCCGCCGG	CCGGCCAATT	GGATTGGCGC	1200
CAGCCGTGAT	TGCCGCGTGA	GCCCCCGAGT	TCCGTCTCCC	GTGCGCGTGG	CATTGTGGAA	1260
GCAATGAACG	AGGCAGAACCA	CAGCGTTGAG	CACCCCTCCCG	TGCAGGGCAG	TTACGTCGAA	1320
GGCGGTGTGG	TCGAGCATCC	GGATGCCAAG	GACTTCGGCA	GCGCCGCCGC	CCTGCCCGCC	1380
GATCCGACCT	GGTTTAAGCA	CGCCGTCTTC	TACGAGGTGC	TGGTCCGGGC	GTTCTTCGAC	1440
GCCAGCGCGG	ACGGTTCCGN	CGATCTCGT	GGACTCATCG	ATCGCCTCGA	CTACCTGCAG	1500
TGGCTTGGCA	TCGACTGCAT	CTGTTGCCGC	CGTTCCCTACG	ACTCACCGCT	GCGCGACGGC	1560
GGTTACGACA	TTCGCGACTT	CTACAAGGTG	CTGCCCGAAT	TCGGCACCGT	CGACGATTTC	1620

GTCGCCCTGG TCGACACCGC TCACCGGCGA GGTATCCGCA TCATCACCGA CCTGGTGATG	1680
AATCACACCT CGGAGTCGCA CCCCTGGTTT CAGGAGTCCC GCCGCGACCC AGACGGACCG	1740
TACGGTGACT ATTACGTGTG GAGCGACACC AGCGAGCGCT ACACCGACGC CCGGATCATC	1800
TTCGTGACA CCGAAGAGTC GAACTGGTCA TTCGATCCTG TCCGCCGACA GTTNCTACTG	1860
GCACCGATTCTT	1872

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1482 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CTTCGCCGAA ACCTGATGCC GAGGAACAGG GTGTTCCCGT GAGCCCGACG GCGTCCGACC	60
CCCGCGCTCCT CGCCGAGATC AGGCAGTCGC TTGATGCGAC AAAAGGGTTG ACCAGCGTGC	120
ACGTAGCGGT CCGAACAAACC GGGAAAGTCG ACAGCTTGCT GGGTATTACC AGTGCCGATG	180
TCGACGTCCG GGCCAATCCG CTCGCGCAA AGGGCGTATG CACCTACAAC GACGAGCAGG	240
GTGTCCCGTT TCGGGTACAA GGCGACAACA TCTCGGTGAA ACTGTTGAC GACTGGAGCA	300
ATCTCGGCTC GATTCTGAA CTGTCAACTT CACGCGTGCT CGATCCTGCC GCTGGGGTGA	360
CGCAGCTGCT GTCCGGTGTAC ACGAACCTCC AAGCGCAAGG TACCGAAGTG ATAGACGGAA	420
TTTCGACCAC CAAAATCACC GGGACCATCC CCGCGAGCTC TGTCAAGATG CTTGATCCTG	480
GCGCCAAGAG TGCAAGGCCG GCGACCCTGT GGATTGCCA GGACGGCTCG CACCACCTCG	540
TCCGAGCGAG CATCGACCTC GGATCCGGGT CGATTAGCT CACGCAGTCG AAATGGAACG	600

AACCCGTCAA CGTCGACTAG GCCGAAGTTG CGTCGACGCG TTGCTCGAAA CGCCCTTGTG	660
AACGGTGTCA ACGGCACCCG AAAACTGACC CCCTGACGGC ATCTGAAAAT TGACCCCCTA	720
GACCGGGCGG T ^T TGGTGGTTA TTCTTCGGTG GTTCCGGCTG GTGGGACGCG GCCGAGGTCG	780
CGGTCTTGAGCGGTAGCT GTCGCCTTG AGGGCGACGA CTTCAGCATG GTGGACGAGG	840
CGGTCGATCA TGGCGGCAGC AACGACGTCG TCGCCGCCGA AAACCTCGCC CCACCGGCCG	900
AAGGCCTTAT TGGACGTGAC GATCAAGCTG GCCCGCTCAT ACCGGGAGGA CACCAGCTGG	960
AAGAAGAGGT TGGCGGCCTC GGGCTAAAC GGAATGTAAC CGACTTCGTC AACCAACCAGG	1020
AGCGGATAGC GGCCAAACCG GGTGAGTTCG GCGTAGATGC GCCCGGCGTG GTGAGCCTCG	1080
GCGAACCGTG CTACCCATTG GGCAGCGGTG GCGAACAGCA CCCGATGACC GGCCTGACAC	1140
GCGCGTATCG CCAGGCCGAC CGCAAGATGA GTCTTCCCGG TGCCAGGCGG GGCCAAAAAA	1200
CACGACGTTA TCGCGGGCGG TGATGAAATC CAGGGTGCCC AGATGTGCGA TGGTGTGCGG	1260
TTTGAGGCCA CGAGCATGCT CAAAGTCGAA CTCTTCCAAC GACTTCCGAA CCGGGAAAGCG	1320
GGCGGCGCGG ATGCGGCCCT CACCACCATG GGACTCCCGG GCTGACACTT CCCGCTGCAG	1380
GCAGGCGGCC AGGTATTCTT CGTGGCTCCA GTTCTCGGCG CGGGCGCGAT CGGCCAGCCG	1440
GGACACTGAC TCACGCAGGG TGGGAGCTTT CAATGCTCTT GT	1482

(2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 876 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GAATTCGGCA CGAGCCGGCG ATAGCTCTG GGCCGCGGCC GACCAGATGG CTCGAGGGTT	60
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CGTGCTCGGG	GCCACCGCCG	GGCGCACCAAC	CCTGACCGGT	GAGGGCCTGC	AACACGCCGA	120
CGGTCACTCG	TGCTGCTGG	ACGCCACCAA	CCC GGCGGTG	GTTGCCTACG	ACCCGGCCTT	180
CGCCTACGAA	ATCGGCTACA	TCGNNGAAAG	CGGACTGGCC	AGGATGTGCG	GGGAGAACCC	240
GGAGAACATC	TTCTTCTACA	TCACCGTCTA	CAACGAGCCG	TACGTGCAGC	CGCCGGAGCC	300
GGAGAACATTC	GATCCCGAGG	GCGTGCTGGG	GGGTATCTAC	CGNTATCACG	CGGCCACCGA	360
GCAACGCACC	AACAAGGNGC	AGATCCTGGC	CTCCGGGGTA	GCGATGCCCG	CGGCGCTGCG	420
GGCAGCACAG	ATGCTGGCCG	CCGAGTGGGA	TGTCGCCGCC	GACGTGTGGT	CGGTGACCAG	480
TTGGGGCGAG	CTAAACCGCG	ACGGGGTGGT	CATCGAGACC	GAGAAGCTCC	GCCACCCCGA	540
TCGGCCGGCG	GGCGTGCCCT	ACGTGACGAG	AGCGCTGGAG	AATGCTCGGG	GCCC GG TGAT	600
CGCGGTGTCG	GACTGGATGC	GCGCGGTCCC	CGAGCAGATC	CGACCGTGGG	TGCCGGGCAC	660
ATACCTCACG	TTGGGCACCG	ACGGGTTCGG	TTTTCCGAC	ACTCGGCCCG	CCGGTCGTCG	720
TTACTTCAAC	ACCGACGCCG	AATCCCAGGT	TGGTCGCGGT	TTTGGGAGGG	GTTGGCCGGG	780
TCGACGGGTG	AATATCGACC	CATTGGTGC	CGGTCGTGGG	CCGCCCGCCC	AGTTACCCGG	840
ATTCGACGAA	GGTGGGGGGT	TGCGCCCGAN	TAAGTT			876

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1021 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

ATCCCCCCGG	GCTGCAGGAA	TTCGGCACGA	GAGACAAAAT	TCCACCGCGTT	AATGCAGGAA	60
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CAGATTATA	ACGAATTAC	AGCGGCACAA	CAATATGTCG	CGATCGCGGT	TTATTCGAC	120
AGCGAAGACC	TGCCGCAGTT	GGCGAACCAT	TTTACAGCC	AAGCGGTCGA	GGAACGAAAC	180
CATGCAATGA	TGCTCGTGCA	ACACCTGCTC	GACCGCGACC	TTCGTGTCGA	AATTCCCGGC	240
GTAGACACGG	TGCGAAACCA	GTTCGACAGA	CCCCGCGAGG	CACTGGCGCT	GGCGCTCGAT	300
CAGGAACGCA	CAGTCACCGA	CCAGGTCGGT	CGGCTGACAG	CGGTGGCCCG	CGACGAGGGC	360
GATTTCTCG	GCGAGCAGTT	CATGCAGTGG	TTCTTGCAAG	AACAGATCGA	AGAGGTGGCC	420
TTGATGGCAA	CCCTGGTGCG	GGTTGCCGAT	CGGGCCGGGG	CCAACCTGTT	CGAGCTAGAG	480
AACTTCGTCG	CACGTGAAGT	GGATGTGGCG	CCGGCCGCAT	CAGGCGCCCC	GCACGCTGCC	540
GGGGGCCGCC	TCTAGATCCC	TGGGGGGGAT	CAGCGAGTGG	TCCCCTTCGC	CCGCCCGTCT	600
TCCAGCCAGG	CCTTGGTGCG	GCCGGGGTGG	TGAGTACCAA	TCCAGGCCAC	CCCGACCTCC	660
CGGNAAAAGT	CGATGTCCTC	GTACTCATCG	ACGTTCCAGG	AGTACACCGC	CCGGCCCTGA	720
GCTGCCGAGC	GGTCAACGAG	TTGCGGATAT	TCCTTTAACG	CAGGCAGTGA	GGGTCCCACG	780
GCGGTTGGCC	CGACCGCCGT	GGCCGCACTG	CTGGTCAGGT	ATCGGGGGGT	CTTGGCGAGC	840
AACAACGTCG	GCAGGGAGGGG	TGGAGCCCGC	CGGATCCGCA	GACCGGGGGG	GCGAAAACGA	900
CATCAACACC	GCACGGGATC	GATCTGCGGA	GGGGGGTGCG	GGAATACCGA	ACCGGTGTAG	960
GAGCGCCAGC	AGTTGTTTTT	CCACCAGCGA	AGCGTTTCG	GGTCATCGGN	GGCNNTTAAG	1020
T						1021

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 321 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CGTGCCGACG AACGGAAGAA CACAACCATG AAGATGGTGA AATCGATCGC CGCAGGTCTG	60
ACCGCCGCGG CTGCAATCGG CGCCGCTGCG GCCGGTGTGA CTTCGATCAT GGCTGGCGGN	120
CCGGTCGTAT ACCAGATGCA GCCGGTCGTC TTCGGCGCGC CACTGCCGTT GGACCCGGNA	180
TCCGCCCTG ANGTCCCGAC CGCCGCCAG TGGACCAGNC TGCTAACAG NCTCGNCGAT	240
CCCAACGTGT CGTTTNGAA CAAGGGNAGT CTGGTCGAGG GNGGNATCGG NGGNANGAG	300
GGNGNGNATC GNCGANCACA A	321

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 373 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TCTTATCGGT TCCGGTTGGC GACGGTTTT GGGNGCGGGT GGTTAACCCG CTCGGCCAGC	60
CGATCGACGG GCGCGGAGAC GTGACTCCG ATACTCGCG CGCGCTGGAG CTCCAGGCAGC	120
CCTCGGTGGT GNACCGGCAA GGC GTGAAGG AGCCGTTGNA GACCGGGATC AAGGCGATTG	180
ACGCGATGAC CCCGATCGGC CGCGGGCAGC GCCAGCTGAT CATCGGGGAC CGCAAGACCG	240
GCAAAAACCG CCGTCTGTGT CGGACACCCT CCTCAAACCA GCGGGAAAGAA CTGGGAGTCC	300
GGTGGATCCC AAGAAGCAGG TGCGCTTGTG TATACTGG CCATCGGGCA AGAAGGGGAA	360
CTTACCATCG CCG	373

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 352 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GTGACGCCGT GATGGGATT C	CTGGGCGGGG CCGGTCCGCT GGCGGTGGTG GATCAGCAAC	60
TGGTTACCCG GGTGCCGCAA GGCTGGTCGT TTGCTCAGGC AGCCGCTGTG CCGGTGGTGT	120	
TCTTGACGGC CTGGTACGGG TTGGCCGATT TAGCCGAGAT CAAGGCGGGC GAATCGGTGC	180	
TGATCCATGC CGGTACCGGC GGTGTGGGCA TGGCGGCTGT GCAGCTGGCT CGCCAGTGGG	240	
GCGTGGAGGT TTTCGTCACC GCCAGCCGTG GNAAGTGGGA CACGCTGCGC GCCATNGNGT	300	
TTGACGACGA NCCATATCGG NGATTCCNC ACATNCGAAG TTCCGANGGA GA	352	

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 726 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GAAATCCGCG TTCATTCCGT TCGACCAGCG GCTGGCGATA ATCGACGAAG TGATCAAGCC	60
GCGGTTCGCG GCGCTCATGG GTCACAGCGA GTAATCAGCA AGTTCTCTGG TATATCGCAC	120
CTAGCGTCCA GTTGCTTGCC AGATCGCTTT CGTACCGTCA TCGCATGTAC CGGTTCGCGT	180
GCCGCACGCT CATGCTGGCG GCGTGCATCC TGGCCACGGG TGTGGCGGGT CTCGGGGTCG	240

GCAGCGCAGTC CGCAGCCAA ACCGCGCCGG TGCCCGACTA CTACTGGTGC CGGGGGCAGC	300
CTTTCGACCC CGCATGGGGG CCCAACTGGG ATCCCTACAC CTGCCATGAC GACTTCCACC	360
GCGACAGCGA CGGCCCGAC CACAGCCGCG ACTACCCCGG ACCCATCCTC GAAGGTCCCG	420
TGCTTGACGA TCCC GG TGCT GCGCCGCCGC CCCCGGCTGC CGGTGGCGGC GCATAGCGCT	480
CGTTGACCGG GCCGCATCAG CGAATACGCG TATAAACCCG GGCGTGCCCC CGGCAAGCTA	540
CGACCCCCGG CGGGGCAGAT TTACGCTCCC GTGCCGATGG ATCGCGCCGT CCGATGACAG	600
AAAATAGGCG ACGGTTTG CAACCGCTTG GAGGACGCTT GAAGGGAACC TGTCATGAAC	660
GGCGACAGCG CCTCCACCAT CGACATCGAC AAGGTTGTTA CCCGCACACC CGTTCGCCGG	720
ATCGTG	726

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 580 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CGCGACGACG ACAGAACGTCG GGCCCACAC CGCCTATGCG TTGATGCAGG CGACCGGGAT	60
GGTCGCCGAC CATATCCAAG CATGCTGGGT GCCCACTGAG CGACCTTTG ACCAGCCGG	120
CTGCCCGATG GCGGCCCGGT GAAGTCATTG CGCCGGGGCT TGTGCACCTG ATGAACCGA	180
ATAGGGAACA ATAGGGGGGT GATTGGCAG TTCAATGTG GGTATGGCTG GAAATCCAAT	240
GGCGGGGCAT GCTCGCGGCC GACCAGGCTC GCGCAGGCGG GCCAGCCGA ATCTGGAGGG	300
AGCACTCAAT GGCGCGATG AAGCCCCGA CCGCGACGG TCCTTGGAA GCAACTAAGG	360

AGGGGCGCGG CATTGTGATG CGAGTACCAAC TTGAGGGTGG CGGTCGCCTG GTCGTCGAGC 420
TGACACCCGA CGAACGCCGC GCACGGGTG ACGAACTCAA AGGCGTTACT AGCTAAGACC 480
AGCCCAACGG CGAATGGTCG GCGTTACGCG CACACCTTCC GGTAGATGTC CAGTGTCTGC 540
TCGGCGATGT ATGCCAGGA GAACTCTTGG ATACAGCGCT 580

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 160 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

AACGGAGGCG CCGGGGGTTT TGGCGGGGCC GGGGCGGTG GCGGCAACGG CGGGGCCGGC 60
GGTACCGCCG GGTTGTTCGG TGTCGGCGGG GCCGGTGGGG CCGGAGGCAA CGGCATCGCC 120
GGTGTACCGG GTACGTCGGC CAGCACACCG GGTGGATCCG 160

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 272 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GACACCGATA CGATGGTGAT GTACGCCAAC GTTGTGACA CGCTCGAGGC GTTCACGATC 60
CAGCGCACAC CCGACGGCGT GACCATCGGC GATGCGGCC CGTTCGCGGA GGCGGCTGCC 120

AAGGCGATGG GAATCGACAA GCTGCGGGTA ATTCAACCG GAATGGACCC CGTCGTCGCT 180
GAACGCGAAC AGTGGGACGA CGGCAACAAC ACGTTGGCGT TGGCGCCCGG TGTCGTTGTC 240
GCCTACGAGC GCAACGTACA GACCAACGCC CG 272

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 317 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

GCAGCCGGTG GTTCTCGGAC TATCTGCGCA CGGTGACGCA GCGCGACGTG CGCGAGCTGA 60
AGCGGATCGA GCAGACGGAT CGCCTGCCGC GGTTCATGCG CTACCTGGCC GCTATCACCG 120
CGCAGGGAGCT GAACGTGGCC GAAGCGGCGC GGGTCATCGG GGTGACGCG GGGACGATCC 180
GTTCGGATCT GGCCTGGTTC GAGACGGTCT ATCTGGTACA TCGCCTGCC GCCTGGTCGC 240
GGAATCTGAC CGCGAAGATC AAGAAGCGGT CAAAGATCCA CGTCGTCGAC AGTGGCTTCG 300
CGGCCTGGTT GCGCGGG 317

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 182 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GATCGTGGAG CTGTCGATGA ACAGCGTTGC CGGACGCGCG GCGGCCAGCA CGTCGGTGTA 60
GCAGCGCCGG ACCACCTCGC CGGTGGCAG CATGGTGATG ACCACGTCGG CCTCGGCCAC 120
CGCTTCGGGC GCGCTACGAA ACACCGCGAC ACCGTGCGCG GCGGCCGG ACGCCGCCGT 180
GG 182

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 308 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GATCGCGAAG TTTGGTGAGC AGGTGGTCGA CGCGAAAGTC TGGGCGCCTG CGAACGGGT 60
CGGCGTTCAC GAGGCGAAGA CACGCCGTGTC CGAGCTGCTG CGGCTCGTCT ACGGCGGGCA 120
GAGGTTGAGA TTGCCCGCCG CGGCGAGCCG GTAGCAAAGC TTGTGCCGCT GCATCCTCAT 180
GAGACTCGGC GGTTAGGCAT TGACCATGGC GTGTACCGCG TGCCGACGA TTTGGACGCT 240
CCGTTGTCAG ACGACGTGCT CGAACGCTTT CACCGGTGAA GCGCTACCTC ATCGACACCC 300
ACGTTTGG 308

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 267 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

CCGACGACGA GCAACTCACG TGGATGATGG TCGGCAGCGG CATTGAGGAC GGAGAGAAC 60
CGGCCGAAGC TGCCGCGCGG CAAGTGCTCA TAGTGACCGG CCGTAGAGGG CTCCCCCGAT 120
GGCACCGGAC TATTCTGGTG TGCCGCTGGC CGGTAAGAGC GGGTAAAAGA ATGTGAGGGG 180
ACACGATGAG CAATCACACC TACCGAGTGA TCGAGATCGT CGGGACCTCG CCCGACGGCG 240
TCGACGCGGC AATCCAGGGC GGTCTGG 267

(2) INFORMATION FOR SEQ ID NO:32:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 189 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CTCGTGCCGA AAGAATGTGA GGGGACACGA TGAGCAATCA CACCTACCGA GTGATCGAGA 60
TCGTCGGGAC CTCGCCCCAC GGCGTCGACG CGGCAATCCA GGGCGGTCTG GCCCGAGCTG 120
CGCAGACCAT GCGCGCGCTG GACTGGTCG AAGTACAGTC AATTGAGGC CACCTGGTCG 180
ACGGAGCGG 189

(2) INFORMATION FOR SEQ ID NO:33:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 851 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CTGCAGGGTG GCGTGGATGA GCGTCACCGC GGGGCAGGCC GAGCTGACCG CCGCCCAGGT	60
CCGGGTTGCT GCGGCGGCCT ACGAGACGGC GTATGGGCTG ACGGTGCCCG CGCCGGTGAT	120
CGCCGAGAAC CGTGCTGAAC TGATGATTCT GATAGCGACC AACCTCTTGG GGCAAAACAC	180
CCCGGCGATC GCGGTCAACG AGGCCGAATA CGGCGAGATG TGGGCCAAG ACGCCGCCGC	240
GATGTTGGC TACGCCGCGG CGACGGCGAC GGCGACGGCG ACGTTGCTGC CGTTCGAGGA	300
GGCGCCGGAG ATGACCAGCG CGGGTGGGCT CCTCGAGCAG GCCGCCGCGG TCGAGGAGGC	360
CTCCGACACC GCCGCGGCGA ACCAGTTGAT GAACAATGTG CCCCAGGCAG TGAAACAGTT	420
GGCCCAGCCC ACGCAGGGCA CCACGCCTTC TTCCAAGCTG GGTGGCCTGT GGAAGACGGT	480
CTCGCCGCAT CGGTCGCCGA TCAGCAACAT GGTGTCGATG GCCAACAAACC ACATGTCGAT	540
GACCAAACAC GGTGTGTCGA TGACCAACAC CTTGAGCTCG ATGTTGAAGG GCTTGCTCC	600
GGCGGCGGCC GCCCAGGCCG TGCAAACCGC GGCGAAAAC GGGGTCCGGG CGATGAGCTC	660
GCTGGGCAGC TCGCTGGGTT CTTCGGGTCT GGGCGGTGGG GTGGCCGCCA ACTTGGGTG	720
GGCGGCCTCG GTACGGTATG GTCACCGGGA TGGCGAAAA TATGCANAGT CTGGTCGGCG	780
GAACGGTGGT CGGGCGTAAG GTTTACCCCC GTTTCTGGA TGCGGTGAAC TTCGTCAACG	840
GAAACAGTTA C	851

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 254 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GATCGATCGG GCGGAAATT GGACCAGATT CGCCTCCGGC GATAACCAA TCAATCGAAC	60
CTAGATTAT TCCGTCCAGG GGCCCGAGTA ATGGCTCGCA GGAGAGGAAC CTTACTGCTG	120
CGGGCACCTG TCGTAGGTCC TCGATACGGC GGAAGGCAGTC GACATTTCC ACCGACACCC	180
CCATCCAAAC GTTCGAGGGC CACTCCAGCT TGTGAGCGAG GCGACGCAGT CGCAGGCTGC	240
GCTTGGTCAA GATC	254

(2) INFORMATION FOR SEQ ID NO:35:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 408 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CGGCACGAGG ATCCTGACCG AAGCGGCCGC CGCCAAGGCG AAGTCGCTGT TGGACCAGGA	60
GGGACGGGAC GATCTGGCGC TGCGGATCGC GGTTCAGCCG GGGGGGTGCG CTGGATTGCG	120
CTATAACCTT TTCTTCGACG ACCGGACGCT GGATGGTGAC CAAACCGCGG AGTCGGTGG	180
TGTCAGGTTG ATCGTGGACC GGATGAGCGC GCCGTATGTG GAAGGCGCGT CGATCGATT	240
CGTCGACACT ATTGAGAAGC AAGGNTTCAC CATCGACAAT CCCAACGCCA CCGGCTCCTG	300
CGCGTGCAGG GATTCGTTCA ACTGATAAAA CGCTAGTACG ACCCCGCGGT GCGAACACG	360
TACGAGCACA CCAAGACCTG ACCCGCGCTGG AAAAGCAACT GAGCGATG	408

(2) INFORMATION FOR SEQ ID NO:36:

- (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 181 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GC GG TG TCGG CG GAT CCG GC GG GT GG TT GA AC GG CA AC GG CG GG CC CG GC GG GG CC GG CG	60
GG ACC CGG CG GC TA AC GG TG GT GC CGG CG CA AC GC CT GG TT GT TC GG GG CC GG CG GG GT CC CG	120
GC GG NG CC CGG CAC CA AT GG GT GG NG TC GG CG GG TC GG CG AT TT GT CT AC GG CA AC GG CG	180
G	181

(2) INFORMATION FOR SEQ ID NO:37:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 290 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GC GG TG TCGG CG GAT CCG GC GG GT GG TT GA AC GG CA AC GG CG GT TG TCG GC GG CC GG GG CG	60
GCG AC GG CG GT CT TT GC CG GT GC CGG CG GC AG GG CG GG CCT CG GT GG GC AG GG CA AT G	120
GC GG CG GCT CAC CGG CG GC AAC GG CG GT C TT GG CG GCG C GG CG GT GG GC GG AG GCA AC G	180
CC CCG GAC GG CG GCT TC GG GT GG CA AC GG CG GT AAG GG GT GG CC AG GG CG GN ATT GG CG GCG	240
GC ACT CAG AG CG CG ACC CG GC CTC GG NG GT TG AC GG CG GT GA CGG CG GT GAC	290

(2) INFORMATION FOR SEQ ID NO:38:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 34 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GATCCAGTGG CATGGNGGGT GTCAGTGGAA GCAT

34

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 155 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GATCGCTGCT CGTCCCCCCC TTGCCGCCGA CGCCACCGGT CCCACCGTTA CCGAACAAAGC 60

TGGCGTGGTC GCCAGCACCC CCGGCACCGC CGACGCCGGA GTCGAACAAT GGCACCGTCG 120

TATCCCCACC ATTGCCGCCG GNCCCACCGG CACCG 155

(2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 53 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

ATGGCGTTCA CGGGGCGCCG GGGACCGGGC AGCCCGGNNG GGCCGGGGGG TGG 53

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GATCCACCGC GGGTGCAGAC GGTGCCCGCG GCGCCACCCC GACCAGCGGC GGCAACGGCG 60

GCACCGGGCGG CAACGGCGCG AACGCCACCG TCGTCGGNNG GGCCGGCGGG GCCGGCGGCA 120

AGGGCGGCCAA CG 132

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GATCGGCGGC CGGNACGGNC GGGGACGGCG GCAAGGGCGG NAACGGGGC GCCGNAGCCA 60

CCNGCCAAGA ATCCTCCGNG TCCNCCAATG GCGCGAATGG CGGACAGGGC GGCAACGGCG 120

GCANCGGCGG CA 132

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 702 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CGGCACGAGG ATCGGTACCC CGCGGCATCG GCAGCTGCCG ATTGCCGGG TTTCCCCACC	60
CGAGGAAAGC CGCTACCAGA TGGCGCTGCC GAAGTAGGGC GATCCGTTCG CGATGCCGGC	120
ATGAACGGGC GGCATCAAAT TAGTGCAGGA ACCTTTCACT TTAGCGACGA TAATGGCTAT	180
AGCACTAAGG AGGATGATCC GATATGACGC AGTCGCAGAC CGTGACGGTG GATCAGCAAG	240
AGATTTGAA CAGGGCCAAC GAGGTGGAGG CCCCGATGGC GGACCCACCG ACTGATGTCC	300
CCATCACACC GTGCGAACTC ACGGNGNTA AAAACGCCGC CCAACAGNTG GTNTTGTCCG	360
CCGACAACAT GCGGGAATAC CTGGCGGCCG GTGCCAAAGA GCGGCAGCGT CTGGCGACCT	420
CGCTGCGCAA CGCGGCCAAG GNGTATGGCG AGGTTGATGA GGAGGCTGCG ACCGCGCTGG	480
ACAACGACGG CGAAGGAAC GTGCAGGCAG AATCGGCCGG GGCCGTCGGA GGGGACAGTT	540
CGGCCGAACT AACCGATACT CCGAGGGTGG CCACGGCCGG TGAACCCAAC TTCATGGATC	600
TCAAAGAACG GGCAAGGAAG CTCGAAACGG GCGACCAAGG CGCATCGCTC GCGCACTGNG	660
GGGATGGGTG GAACACTTNC ACCCTGACGC TGCAAGGCGA CG	702

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 298 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GAAGCCGCAG CGCTGTCGGG CGACGTGGCG GTCAAAGCGG CATCGCTCGG TGGCGGTGGA 60
GGCGGCGGGG TGCCGTCGGC GCCGTTGGGA TCCGCGATCG GGGGCGCCGA ATCGGTGCGG 120
CCCGCTGGCG CTGGTGACAT TGCCGGCTTA GGCCAGGGAA GGGCCGGCGG CGGCGCCGCG 180
CTGGGCGGCG GTGGCATGGG AATGCCGATG GGTGCCGCGC ATCAGGGACA AGGGGGCGCC 240
AAGTCCAAGG GTTCTCAGCA GGAAGACGAG GCGCTCTACA CCGAGGATCC TCGTGCCG 298

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1058 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CGGCACGAGG ATCGAACATCGC GTCGCCGGGA GCACAGCGTC GCACTGCACC AGTGGAGGAG 60
CCATGACCTA CTCGCCGGGT AACCCCGGAT ACCCGCAAGC GCAGCCCGCA GGCTCCTACG 120
GAGGCGTCAC ACCCTCGTTC GCCCACGCCG ATGAGGGTGC GAGCAAGCTA CCGATGTACC 180
TGAACATCGC GGTGGCAGTG CTCGGTCTGG CTGGTACTT CGCCAGCTTC GGCCCAATGT 240
TCACCCCTCAG TACCGAACTC GGGGGGGGTG ATGGCGCAGT GTCCGGTGAC ACTGGGCTGC 300
CGGTCGGGGT GGCTCTGCTG GCTGCGCTGC TTGCCGGGT GGTTCTGGTG CCTAAGGCCA 360
AGAGCCATGT GACGGTAGTT GCGGTGCTCG GGGTACTCGG CGTATTCTG ATGGTCTCGG 420

CGACGTTAA CAAGCCCAGC GCCTATTGA CCGGTTGGGC ATTGTGGGTT GTGTTGGCTT	480
TCATCGTGTT CCAGGCGGTT GCGGCAGTCC TGGCGCTCTT GGTGGAGACC GGCGCTATCA	540
CCGCGCCGGC GCCGCGGCC AAGTCGACC CGTATGGACA GTACGGGCGG TACGGGCAGT	600
ACGGGCAGTA CGGGGTGCAG CCGGGTGGGT ACTACGGTCA GCAGGGTGCT CAGCAGGCCG	660
CGGGACTGCA GTCGCCCGGC CCGCAGCAGT CTCCGCAGCC TCCCGGATAT GGGTCGCAGT	720
ACGGCGGCTA TTCGTCCAGT CCGAGCCAAT CGGGCAGTGG ATACACTGCT CAGCCCCCGG	780
CCCAGCCGCC GGCGCAGTCC GGGTCGCAAC AATCGCACCA GGGCCCATCC ACGCCACCTA	840
CCGGCTTCC GAGCTTCAGC CCACCAACCAC CGGTCAGTGC CGGGACGGGG TCGCAGGCTG	900
GTTCGGCTCC AGTCAACTAT TCAAACCCCA GCGGGGGCGA GCAGTCGTCG TCCCCCGGGG	960
GGGCGCCGGT CTAACCGGGC GTTCCCGCGT CCGGTCGCGC GTGTGCGCGA AGAGTGAACA	1020
GGGTGTCAGC AAGCGCGGAC GATCCTCGTG CCGAATT	1058

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 327 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CGGCACGAGA GACCGATGCC GCTACCCCTCG CGCAGGAGGC AGGTAATTTC GAGCGGATCT	60
CCGGCGACCT GAAAACCCAG ATCGACCAGG TGGAGTCGAC GGCAGGTTCG TTGCAGGGCC	120
AGTGGCGCGG CGCGGCGGGG ACGGCCGCC AGGCCGCGGT GGTGCGCTTC CAAGAACGAG	180
CCAATAAGCA GAAGCAGGAA CTCGACGAGA TCTCGACGAA TATTCGTCAG GCCGGCGTCC	240
AATACTCGAG GGCCGACGAG GAGCAGCAGC AGGCAGCTGTC CTCGCAAATG GGCTTCTGAC	300

CCGCTAATAC GAAAAGAAAC GGAGCAA 327

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 170 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CGGTGCGCAT GATGGCGTTG TCGAACGTGA CCGATTCTGT ACCGCCGTCG TTGAGATCAA 60

CCAACAACGT GTTGGCGTCG GCAAATGTGC CGNACCCGTG GATCTCGGTG ATCTTGTCT 120

TCTTCATCAG GAAGTGCACA CGGGCCACCC TGCCCTCGGN TACCTTCGG 170

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 127 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GATCCGGCGG CACGGGGGGT GCCGGCGGCA GCACCGCTGG CGCTGGCGGC AACGGCGGGG 60

CCGGGGGTGG CGGCGGAACC GGTGGGTTGC TCTTCGGCAA CGGCGGTGCC GGCGGGCACG 120

GGGCCGT 127

(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 81 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CGGCAGGCAAG GGCAGGACCCG CCGGCAACGG GAGCGGCGCG GCCGGCGGCA ACGGCAGCAA	60
CGGCAGGCTCC GGCCTCAACG G	81

(2) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 149 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GATCAGGGCT GGCCGGCTCC GGCCAGAAGG GCGGTAACGG AGGAGCTGCC GGATTGTTTG	60
GCAACGGCGG GGCCGGNGGT GCGGCGCGT CCAACCAAGC CGGTAACGGC GGNGCCGGCG	120
GAAACGGTGG TGCCGGTGGG CTGATCTGG	149

(2) INFORMATION FOR SEQ ID NO:51:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 355 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CGGCACGAGA TCACACCTAC CGAGTGATCG AGATCGTCGG GACCTCGCCC GACGGTGTG	60
ACGCGGNAAT CCAGGGCGGT CTGGCCCGAG CTGCGCAGAC CATGCGCGCG CTGGACTGGT	120
TCGAAGTACA GTCAATTGCA GGCCACCTGG TCGACGGAGC GGTCGCGCAC TTCCAGGTGA	180
CTATGAAAGT CGGCTTCCGC CTGGAGGATT CCTGAACCTT CAAGCGCGC CGATAACTGA	240
GGTGCATCAT TAAGCGACTT TTCCAGAACCA TCCTGACGCG CTCGAAACGC GGTTCAGCCG	300
ACGGTGGCTC CGCCGAGGCG CTGCCTCCAA AATCCCTGCG ACAATTGTC GGC	355

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 999 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

ATGCATCACC ATCACCATCA CATGCATCAG GTGGACCCA ACTTGACACG TCGCAAGGGA	60
CGATTGGCGG CACTGGCTAT CGCGGCGATG GCCAGCGCCA GCCTGGTGAC CGTTGCGGTG	120
CCCGCGACCG CCAACGCCGA TCCGGAGCCA GCGCCCCCGG TACCCACAAC GGCCGCCTCG	180
CCGCCGTCGA CCGCTGCAGC GCCACCCGCA CCGGCGACAC CTGTTGCCCG CCCACCACCG	240
GCCGCCGCCA ACACGCCGAA TGCCCAGCCG GGCATCCCA ACGCAGCACC TCCGCCGGCC	300
GACCCGAACG CACCGCCGCC ACCTGTCATT GCCCAAACG CACCCAAACC TGTCCGGATC	360
GACAACCCGG TTGGAGGATT CAGCTTCGCG CTGCCTGCTG GCTGGGTGGA GTCTGACGCC	420

GCCCACCTCG ACTACGGTTC AGCACTCCTC AGCAAAACCA CCGGGGACCC GCCATTTCCC	480
GGACAGCCGC CGCCGGTGGC CAATGACACC CGTATCGTGC TCGGCCGGCT AGACCAAAAG	540
CTTTACGCCA GCGCCGAAGC CACCGACTCC AAGGCCGCGG CCCGGTTGGG CTCGGACATG	600
GGTGAGTTCT ATATGCCCTA CCCGGGCACC CGGATCAACC AGGAAACCGT CTCGCTCGAC	660
GCCAACGGGG TGTCTGGAAG CGCGTCGTAT TACGAAGTCA AGTTCAGCGA TCCGAGTAAG	720
CCGAACGGCC AGATCTGGAC GGGCGTAATC GGCTCGCCCG CGGCGAACGC ACCGGACGCC	780
GGGCCCCCTC AGCGCTGGTT TGTGGTATGG CTCGGGACCG CCAACAACCC GGTGGACAAG	840
GGCGCGGCCA AGGCCTGGC CGAACATCGATC CGGCCTTGG TCGCCCCGCC GCCGGCGCCG	900
GCACCGGCTC CTGCAGAGCC CGCTCCGGCG CGGGCGCCGG CCGGGGAAAGT CGCTCCTACC	960
CCGACGACAC CGACACCGCA GCGGACCTA CGGGCCTGA	999

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 332 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Met His His His His His Met His Gln Val Asp Pro Asn Leu Thr			
1	5	10	15
Arg Arg Lys Gly Arg Leu Ala Ala Leu Ala Ile Ala Ala Met Ala Ser			
20	25	30	
Ala Ser Leu Val Thr Val Ala Val Pro Ala Thr Ala Asn Ala Asp Pro			
35	40	45	
Glu Pro Ala Pro Pro Val Pro Thr Thr Ala Ala Ser Pro Pro Ser Thr			
50	55	60	

Ala Ala Ala Pro Pro Ala Pro Ala Thr Pro Val Ala Pro Pro Pro Pro
65 70 75 80

Ala Ala Ala Asn Thr Pro Asn Ala Gln Pro Gly Asp Pro Asn Ala Ala
85 90 95

Pro Pro Pro Ala Asp Pro Asn Ala Pro Pro Pro Pro Val Ile Ala Pro
100 105 110

Asn Ala Pro Gln Pro Val Arg Ile Asp Asn Pro Val Gly Gly Phe Ser
115 120 125

Phe Ala Leu Pro Ala Gly Trp Val Glu Ser Asp Ala Ala His Phe Asp
130 135 140

Tyr Gly Ser Ala Leu Leu Ser Lys Thr Thr Gly Asp Pro Pro Phe Pro
145 150 155 160

Gly Gln Pro Pro Pro Val Ala Asn Asp Thr Arg Ile Val Leu Gly Arg
165 170 175

Leu Asp Gln Lys Leu Tyr Ala Ser Ala Glu Ala Thr Asp Ser Lys Ala
180 185 190

Ala Ala Arg Leu Gly Ser Asp Met Gly Glu Phe Tyr Met Pro Tyr Pro
195 200 205

Gly Thr Arg Ile Asn Gln Glu Thr Val Ser Leu Asp Ala Asn Gly Val
210 215 220

Ser Gly Ser Ala Ser Tyr Tyr Glu Val Lys Phe Ser Asp Pro Ser Lys
225 230 235 240

Pro Asn Gly Gln Ile Trp Thr Gly Val Ile Gly Ser Pro Ala Ala Asn
245 250 255

Ala Pro Asp Ala Gly Pro Pro Gln Arg Trp Phe Val Val Trp Leu Gly
260 265 270

Thr Ala Asn Asn Pro Val Asp Lys Gly Ala Ala Lys Ala Leu Ala Glu
275 280 285

Ser Ile Arg Pro Leu Val Ala Pro Pro Pro Ala Pro Ala Pro Ala Pro
290 295 300

Ala Glu Pro Ala Pro Ala Pro Ala Pro Ala Gly Glu Val Ala Pro Thr
305 310 315 320

Pro Thr Thr Pro Thr Pro Gln Arg Thr Leu Pro Ala
325 330

(2) INFORMATION FOR SEQ ID NO:54:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 20 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Asp Pro Val Asp Ala Val Ile Asn Thr Thr Xaa Asn Tyr Gly Gln Val
1 5 10 15

Val Ala Ala Leu
20

(2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Ala Val Glu Ser Gly Met Leu Ala Leu Gly Thr Pro Ala Pro Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Ala	Ala	Met	Lys	Pro	Arg	Thr	Gly	Asp	Gly	Pro	Leu	Glu	Ala	Ala	Lys
1				5					10				15		
Glu Gly Arg															

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Tyr	Tyr	Trp	Cys	Pro	Gly	Gln	Pro	Phe	Asp	Pro	Ala	Trp	Gly	Pro
1				5					10				15	

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Asp Ile Gly Ser Glu Ser Thr Glu Asp Gln Gln Xaa Ala Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Ala Glu Glu Ser Ile Ser Thr Xaa Glu Xaa Ile Val Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Asp Pro Glu Pro Ala Pro Pro Val Pro Thr Ala Ala Ala Ala Pro Pro
1 5 10 15

Ala

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Ala	Pro	Lys	Thr	Tyr	Xaa	Glu	Glu	Leu	Lys	Gly	Thr	Asp	Thr	Gly
1					5				10					15

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Asp	Pro	Ala	Ser	Ala	Pro	Asp	Val	Pro	Thr	Ala	Ala	Gln	Gln	Thr	Ser
1					5				10					15	

Leu	Leu	Asn	Asn	Leu	Ala	Asp	Pro	Asp	Val	Ser	Phe	Ala	Asp		
					20				25				30		

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 187 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Thr Gly Ser Leu Asn Gln Thr His Asn Arg Arg Ala Asn Glu Arg Lys
1 5 10 15

Asn Thr Thr Met Lys Met Val Lys Ser Ile Ala Ala Gly Leu Thr Ala
20 25 30

Ala Ala Ala Ile Gly Ala Ala Ala Gly Val Thr Ser Ile Met Ala
35 40 45

Gly Gly Pro Val Val Tyr Gln Met Gln Pro Val Val Phe Gly Ala Pro
50 55 60

Leu Pro Leu Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln
65 70 75 80

Leu Thr Ser Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala
85 90 95

Asn Lys Gly Ser Leu Val Glu Gly Gly Ile Gly Thr Glu Ala Arg
100 105 110

Ile Ala Asp His Lys Leu Lys Lys Ala Ala Glu His Gly Asp Leu Pro
115 120 125

Leu Ser Phe Ser Val Thr Asn Ile Gln Pro Ala Ala Gly Ser Ala
130 135 140

Thr Ala Asp Val Ser Val Ser Gly Pro Lys Leu Ser Ser Pro Val Thr
145 150 155 160

Gln Asn Val Thr Phe Val Asn Gln Gly Gly Trp Met Leu Ser Arg Ala
165 170 175

Ser Ala Met Glu Leu Leu Gln Ala Ala Gly Xaa
180 185

(2) INFORMATION FOR SEQ ID NO:64:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 148 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Asp Glu Val Thr Val Glu Thr Thr Ser Val Phe Arg Ala Asp Phe Leu
1 5 10 15

Ser Glu Leu Asp Ala Pro Ala Gln Ala Gly Thr Glu Ser Ala Val Ser
20 25 30

Gly Val Glu Gly Leu Pro Pro Gly Ser Ala Leu Leu Val Val Lys Arg
35 40 45

Gly Pro Asn Ala Gly Ser Arg Phe Leu Leu Asp Gln Ala Ile Thr Ser
50 55 60

Ala Gly Arg His Pro Asp Ser Asp Ile Phe Leu Asp Asp Val Thr Val
65 70 75 80

Ser Arg Arg His Ala Glu Phe Arg Leu Glu Asn Asn Glu Phe Asn Val
85 90 95

Val Asp Val Gly Ser Leu Asn Gly Thr Tyr Val Asn Arg Glu Pro Val
100 105 110

Asp Ser Ala Val Leu Ala Asn Gly Asp Glu Val Gln Ile Gly Lys Leu
115 120 125

Arg Leu Val Phe Leu Thr Gly Pro Lys Gln Gly Glu Asp Asp Gly Ser
130 135 140

Thr Gly Gly Pro
145

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 230 amino acids

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Thr Ser Asn Arg Pro Ala Arg Arg Gly Arg Arg Ala Pro Arg Asp Thr
1 5 10 15

Gly Pro Asp Arg Ser Ala Ser Leu Ser Leu Val Arg His Arg Arg Gln
20 25 30

Gln Arg Asp Ala Leu Cys Leu Ser Ser Thr Gln Ile Ser Arg Gln Ser
35 40 45

Asn Leu Pro Pro Ala Ala Gly Gly Ala Ala Asn Tyr Ser Arg Arg Asn
50 55 60

Phe Asp Val Arg Ile Lys Ile Phe Met Leu Val Thr Ala Val Val Leu
65 70 75 80

Leu Cys Cys Ser Gly Val Ala Thr Ala Ala Pro Lys Thr Tyr Cys Glu
85 90 95

Glu Leu Lys Gly Thr Asp Thr Gly Gln Ala Cys Gln Ile Gln Met Ser
100 105 110

Asp Pro Ala Tyr Asn Ile Asn Ile Ser Leu Pro Ser Tyr Tyr Pro Asp
115 120 125

Gln Lys Ser Leu Glu Asn Tyr Ile Ala Gln Thr Arg Asp Lys Phe Leu
130 135 140

Ser Ala Ala Thr Ser Ser Thr Pro Arg Glu Ala Pro Tyr Glu Leu Asn
145 150 155 160

Ile Thr Ser Ala Thr Tyr Gln Ser Ala Ile Pro Pro Arg Gly Thr Gln
165 170 175

Ala Val Val Leu Xaa Val Tyr His Asn Ala Gly Gly Thr His Pro Thr
180 185 190

Thr Thr Tyr Lys Ala Phe Asp Trp Asp Gln Ala Tyr Arg Lys Pro Ile
195 200 205

Thr Tyr Asp Thr Leu Trp Gln Ala Asp Thr Asp Pro Leu Pro Val Val
210 215 220

Phe Pro Ile Val Ala Arg
225 230

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 132 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Thr Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gly Gln Gly Phe
1 5 10 15

Ala Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser
20 25 30

Gly Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly
35 40 45

Leu Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val
50 55 60

Val Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val
65 70 75 80

Ile Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala
85 90 95

Asp Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp
100 105 110

Gln Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu
115 120 125
Gly Pro Pro Ala
130

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 100 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Val Pro Leu Arg Ser Pro Ser Met Ser Pro Ser Lys Cys Leu Ala Ala
1 5 10 15
Ala Gln Arg Asn Pro Val Ile Arg Arg Arg Arg Leu Ser Asn Pro Pro
20 25 30
Pro Arg Lys Tyr Arg Ser Met Pro Ser Pro Ala Thr Ala Ser Ala Gly
35 40 45
Met Ala Arg Val Arg Arg Ala Ile Trp Arg Gly Pro Ala Thr Xaa
50 55 60
Ser Ala Gly Met Ala Arg Val Arg Arg Trp Xaa Val Met Pro Xaa Val
65 70 75 80
Ile Gln Ser Thr Xaa Ile Arg Xaa Xaa Gly Pro Phe Asp Asn Arg Gly
85 90 95
Ser Glu Arg Lys
100

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 163 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Met Thr Asp Asp Ile Leu Leu Ile Asp Thr Asp Glu Arg Val Arg Thr
1 5 10 15

Leu Thr Leu Asn Arg Pro Gln Ser Arg Asn Ala Leu Ser Ala Ala Leu
20 25 30

Arg Asp Arg Phe Phe Ala Xaa Leu Xaa Asp Ala Glu Xaa Asp Asp Asp
35 40 45

Ile Asp Val Val Ile Leu Thr Gly Ala Asp Pro Val Phe Cys Ala Gly
50 55 60

Leu Asp Leu Lys Val Ala Gly Arg Ala Asp Arg Ala Ala Gly His Leu
65 70 75 80

Thr Ala Val Gly Gly His Asp Gln Ala Gly Asp Arg Arg Asp Gln Arg
85 90 95

Arg Arg Gly His Arg Arg Ala Arg Thr Gly Ala Val Leu Arg His Pro
100 105 110

Asp Arg Leu Arg Ala Arg Pro Leu Arg Arg His Pro Arg Pro Gly Gly
115 120 125

Ala Ala Ala His Leu Gly Thr Gln Cys Val Leu Ala Ala Lys Gly Arg
130 135 140

His Arg Xaa Gly Pro Val Asp Glu Pro Asp Arg Arg Leu Pro Val Arg
145 150 155 160

Asp Arg Arg

(2) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 344 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Met Lys Phe Val Asn His Ile Glu Pro Val Ala Pro Arg Arg Ala Gly
1 5 10 15

Gly Ala Val Ala Glu Val Tyr Ala Glu Ala Arg Arg Glu Phe Gly Arg
20 25 30

Leu Pro Glu Pro Leu Ala Met Leu Ser Pro Asp Glu Gly Leu Leu Thr
35 40 45

Ala Gly Trp Ala Thr Leu Arg Glu Thr Leu Leu Val Gly Gln Val Pro
50 55 60

Arg Gly Arg Lys Glu Ala Val Ala Ala Val Ala Ala Ser Leu Arg
65 70 75 80

Cys Pro Trp Cys Val Asp Ala His Thr Thr Met Leu Tyr Ala Ala Gly
85 90 95

Gln Thr Asp Thr Ala Ala Ala Ile Leu Ala Gly Thr Ala Pro Ala Ala
100 105 110

Gly Asp Pro Asn Ala Pro Tyr Val Ala Trp Ala Ala Gly Thr Gly Thr
115 120 125

Pro Ala Gly Pro Pro Ala Pro Phe Gly Pro Asp Val Ala Ala Glu Tyr
130 135 140

Leu Gly Thr Ala Val Gln Phe His Phe Ile Ala Arg Leu Val Leu Val
145 150 155 160

Leu Leu Asp Glu Thr Phe Leu Pro Gly Gly Pro Arg Ala Gln Gln Leu
165 170 175

100

Met Arg Arg Ala Gly Gly Leu Val Phe Ala Arg Lys Val Arg Ala Glu
180 185 190

His Arg Pro Gly Arg Ser Thr Arg Arg Leu Glu Pro Arg Thr Leu Pro
195 200 205

Asp Asp Leu Ala Trp Ala Thr Pro Ser Glu Pro Ile Ala Thr Ala Phe
210 215 220

Ala Ala Leu Ser His His Leu Asp Thr Ala Pro His Leu Pro Pro Pro
225 230 235 240

Thr Arg Gln Val Val Arg Arg Val Val Gly Ser Trp His Gly Glu Pro
245 250 255

Met Pro Met Ser Ser Arg Trp Thr Asn Glu His Thr Ala Glu Leu Pro
260 265 270

Ala Asp Leu His Ala Pro Thr Arg Leu Ala Leu Leu Thr Gly Leu Ala
275 280 285

Pro His Gln Val Thr Asp Asp Asp Val Ala Ala Ala Arg Ser Leu Leu
290 295 300

Asp Thr Asp Ala Ala Leu Val Gly Ala Leu Ala Trp Ala Ala Phe Thr
305 310 315 320

Ala Ala Arg Arg Ile Gly Thr Trp Ile Gly Ala Ala Ala Glu Gly Gln
325 330 335

Val Ser Arg Gln Asn Pro Thr Gly
340

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 485 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Asp Asp Pro Asp Met Pro Gly Thr Val Ala Lys Ala Val Ala Asp Ala
1 5 10 15

Leu Gly Arg Gly Ile Ala Pro Val Glu Asp Ile Gln Asp Cys Val Glu
20 25 30

Ala Arg Leu Gly Glu Ala Gly Leu Asp Asp Val Ala Arg Val Tyr Ile
35 40 45

Ile Tyr Arg Gln Arg Arg Ala Glu Leu Arg Thr Ala Lys Ala Leu Leu
50 55 60

Gly Val Arg Asp Glu Leu Lys Leu Ser Leu Ala Ala Val Thr Val Leu
65 70 75 80

Arg Glu Arg Tyr Leu Leu His Asp Glu Gln Gly Arg Pro Ala Glu Ser
85 90 95

Thr Gly Glu Leu Met Asp Arg Ser Ala Arg Cys Val Ala Ala Glu
100 105 110

Asp Gln Tyr Glu Pro Gly Ser Ser Arg Arg Trp Ala Glu Arg Phe Ala
115 120 125

Thr Leu Leu Arg Asn Leu Glu Phe Leu Pro Asn Ser Pro Thr Leu Met
130 135 140

Asn Ser Gly Thr Asp Leu Gly Leu Leu Ala Gly Cys Phe Val Leu Pro
145 150 155 160

Ile Glu Asp Ser Leu Gln Ser Ile Phe Ala Thr Leu Gly Gln Ala Ala
165 170 175

Glu Leu Gln Arg Ala Gly Gly Thr Gly Tyr Ala Phe Ser His Leu
180 185 190

Arg Pro Ala Gly Asp Arg Val Ala Ser Thr Gly Gly Thr Ala Ser Gly
195 200 205

Pro Val Ser Phe Leu Arg Leu Tyr Asp Ser Ala Ala Gly Val Val Ser
210 215 220

102

Met Gly Gly Arg Arg Arg Gly Ala Cys Met Ala Val Leu Asp Val Ser
225 230 235 240

His Pro Asp Ile Cys Asp Phe Val Thr Ala Lys Ala Glu Ser Pro Ser
245 250 255

Glu Leu Pro His Phe Asn Leu Ser Val Gly Val Thr Asp Ala Phe Leu
260 265 270

Arg Ala Val Glu Arg Asn Gly Leu His Arg Leu Val Asn Pro Arg Thr
275 280 285

Gly Lys Ile Val Ala Arg Met Pro Ala Ala Glu Leu Phe Asp Ala Ile
290 295 300

Cys Lys Ala Ala His Ala Gly Gly Asp Pro Gly Leu Val Phe Leu Asp
305 310 315 320

Thr Ile Asn Arg Ala Asn Pro Val Pro Gly Arg Gly Arg Ile Glu Ala
325 330 335

Thr Asn Pro Cys Gly Glu Val Pro Leu Leu Pro Tyr Glu Ser Cys Asn
340 345 350

Leu Gly Ser Ile Asn Leu Ala Arg Met Leu Ala Asp Gly Arg Val Asp
355 360 365

Trp Asp Arg Leu Glu Glu Val Ala Gly Val Ala Val Arg Phe Leu Asp
370 375 380

Asp Val Ile Asp Val Ser Arg Tyr Pro Phe Pro Glu Leu Gly Glu Ala
385 390 395 400

Ala Arg Ala Thr Arg Lys Ile Gly Leu Gly Val Met Gly Leu Ala Glu
405 410 415

Leu Leu Ala Ala Leu Gly Ile Pro Tyr Asp Ser Glu Glu Ala Val Arg
420 425 430

Leu Ala Thr Arg Leu Met Arg Arg Ile Gln Gln Ala Ala His Thr Ala
435 440 445

Ser Arg Arg Leu Ala Glu Glu Arg Gly Ala Phe Pro Ala Phe Thr Asp
450 455 460

103

Ser Arg Phe Ala Arg Ser Gly Pro Arg Arg Asn Ala Gln Val Thr Ser
465 470 475 480
Val Ala Pro Thr Gly
485

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 267 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Gly Val Ile Val Leu Asp Leu Glu Pro Arg Gly Pro Leu Pro Thr Glu
1 5 10 15

Ile Tyr Trp Arg Arg Arg Gly Leu Ala Leu Gly Ile Ala Val Val Val
20 25 30

Val Gly Ile Ala Val Ala Ile Val Ile Ala Phe Val Asp Ser Ser Ala
35 40 45

Gly Ala Lys Pro Val Ser Ala Asp Lys Pro Ala Ser Ala Gln Ser His
50 55 60

Pro Gly Ser Pro Ala Pro Gln Ala Pro Gln Pro Ala Gly Gln Thr Glu
65 70 75 80

Gly Asn Ala Ala Ala Pro Pro Gln Gly Gln Asn Pro Glu Thr Pro
85 90 95

Thr Pro Thr Ala Ala Val Gln Pro Pro Pro Val Leu Lys Glu Gly Asp
100 105 110

Asp Cys Pro Asp Ser Thr Leu Ala Val Lys Gly Leu Thr Asn Ala Pro
115 120 125

Gln Tyr Tyr Val Gly Asp Gln Pro Lys Phe Thr Met Val Val Thr Asn

104

130

135

140

Ile Gly Leu Val Ser Cys Lys Arg Asp Val Gly Ala Ala Val Leu Ala
145 - 150 155 160

Ala Tyr Val Tyr Ser Leu Asp Asn Lys Arg Leu Trp Ser Asn Leu Asp
165 170 175

Cys Ala Pro Ser Asn Glu Thr Leu Val Lys Thr Phe Ser Pro Gly Glu
180 185 190

Gln Val Thr Thr Ala Val Thr Trp Thr Gly Met Gly Ser Ala Pro Arg
195 200 205

Cys Pro Leu Pro Arg Pro Ala Ile Gly Pro Gly Thr Tyr Asn Leu Val
210 215 220

Val Gln Leu Gly Asn Leu Arg Ser Leu Pro Val Pro Phe Ile Leu Asn
225 230 235 240

Gln Pro Pro Pro Pro Gly Pro Val Pro Ala Pro Gly Pro Ala Gln
245 250 255

Ala Pro Pro Pro Glu Ser Pro Ala Gln Gly Gly
260 265

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 97 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly Val Gln Val
1 5 10 15

Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu Val Val Ala
20 25 30

105

Gly Gly Ala Ala Ala Asn Ala Gly Val Pro Lys Gly Val Val Val Thr
35 40 45

Lys Val Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu Val Ala Ala
50 55 60

Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr Phe Gln Asp
65 70 75 80

Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly Lys Ala Glu
85 90 95

Gln

(2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 364 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Gly Ala Ala Val Ser Leu Leu Ala Ala Gly Thr Leu Val Leu Thr Ala
1 5 10 15

Cys Gly Gly Gly Thr Asn Ser Ser Ser Ser Gly Ala Gly Gly Thr Ser
20 25 30

Gly Ser Val His Cys Gly Gly Lys Lys Glu Leu His Ser Ser Gly Ser
35 40 45

Thr Ala Gln Glu Asn Ala Met Glu Gln Phe Val Tyr Ala Tyr Val Arg
50 55 60

Ser Cys Pro Gly Tyr Thr Leu Asp Tyr Asn Ala Asn Gly Ser Gly Ala
65 70 75 80

106

Gly Val Thr Gln Phe Leu Asn Asn Glu Thr Asp Phe Ala Gly Ser Asp
85 90 95

Val Pro Leu Asn Pro Ser Thr Gly Gln Pro Asp Arg Ser Ala Glu Arg
100 105 110

Cys Gly Ser Pro Ala Trp Asp Leu Pro Thr Val Phe Gly Pro Ile Ala
115 120 125

Ile Thr Tyr Asn Ile Lys Gly Val Ser Thr Leu Asn Leu Asp Gly Pro
130 135 140

Thr Thr Ala Lys Ile Phe Asn Gly Thr Ile Thr Val Trp Asn Asp Pro
145 150 155 160

Gln Ile Gln Ala Leu Asn Ser Gly Thr Asp Leu Pro Pro Thr Pro Ile
165 170 175

Ser Val Ile Phe Arg Ser Asp Lys Ser Gly Thr Ser Asp Asn Phe Gln
180 185 190

Lys Tyr Leu Asp Gly Val Ser Asn Gly Ala Trp Gly Lys Gly Ala Ser
195 200 205

Glu Thr Phe Ser Gly Gly Val Gly Val Gly Ala Ser Gly Asn Asn Gly
210 215 220

Thr Ser Ala Leu Leu Gln Thr Thr Asp Gly Ser Ile Thr Tyr Asn Glu
225 230 235 240

Trp Ser Phe Ala Val Gly Lys Gln Leu Asn Met Ala Gln Ile Ile Thr
245 250 255

Ser Ala Gly Pro Asp Pro Val Ala Ile Thr Thr Glu Ser Val Gly Lys
260 265 270

Thr Ile Ala Gly Ala Lys Ile Met Gly Gln Gly Asn Asp Leu Val Leu
275 280 285

Asp Thr Ser Ser Phe Tyr Arg Pro Thr Gln Pro Gly Ser Tyr Pro Ile
290 295 300

Val Leu Ala Thr Tyr Glu Ile Val Cys Ser Lys Tyr Pro Asp Ala Thr
305 310 315 320

107

Thr Gly Thr Ala Val Arg Ala Phe Met Gln Ala Ala Ile Gly Pro Gly
325 330 335
Gln Glu Gly Leu Asp Gln Tyr Gly Ser Ile Pro Leu Pro Lys Ser Phe
340 345 350
Gln Ala Lys Leu Ala Ala Ala Val Asn Ala Ile Ser
355 360

(2) INFORMATION FOR SEQ ID NO:74:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 309 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Gln Ala Ala Ala Gly Arg Ala Val Arg Arg Thr Gly His Ala Glu Asp
1 5 10 15
Gln Thr His Gln Asp Arg Leu His His Gly Cys Arg Arg Ala Ala Val
20 25 30
Val Val Arg Gln Asp Arg Ala Ser Val Ser Ala Thr Ser Ala Arg Pro
35 40 45
Pro Arg Arg His Pro Ala Gln Gly His Arg Arg Arg Val Ala Pro Ser
50 55 60
Gly Gly Arg Arg Arg Pro His Pro His His Val Gln Pro Asp Asp Arg
65 70 75 80
Arg Asp Arg Pro Ala Leu Leu Asp Arg Thr Gln Pro Ala Glu His Pro
85 90 95
Asp Pro His Arg Arg Gly Pro Ala Asp Pro Gly Arg Val Arg Gly Arg
100 105 110
Gly Arg Leu Arg Arg Val Asp Asp Gly Arg Leu Gln Pro Asp Arg Asp

108

115	120	125
Ala Asp His Gly Ala Pro Val Arg Gly Arg Gly Pro His Arg Gly Val		
130	135	140
Gln His Arg Gly Gly Pro Val Phe Val Arg Arg Val Pro Gly Val Arg		
145	150	155
Cys Ala His Arg Arg Gly His Arg Arg Val Ala Ala Pro Gly Gln Gly		
165	170	175
Asp Val Leu Arg Ala Gly Leu Arg Val Glu Arg Leu Arg Pro Val Ala		
180	185	190
Ala Val Glu Asn Leu His Arg Gly Ser Gln Arg Ala Asp Gly Arg Val		
195	200	205
Phe Arg Pro Ile Arg Arg Gly Ala Arg Leu Pro Ala Arg Arg Ser Arg		
210	215	220
Ala Gly Pro Gln Gly Arg Leu His Leu Asp Gly Ala Gly Pro Ser Pro		
225	230	235
Leu Pro Ala Arg Ala Gly Gln Gln Pro Ser Ser Ala Gly Gly Arg		
245	250	255
Arg Ala Gly Gly Ala Glu Arg Ala Asp Pro Gly Gln Arg Gly Arg His		
260	265	270
His Gln Gly Gly His Asp Pro Gly Arg Gln Gly Ala Gln Arg Gly Thr		
275	280	285
Ala Gly Val Ala His Ala Ala Gly Pro Arg Arg Ala Ala Val Arg		
290	295	300
Asn Arg Pro Arg Arg		
305		

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 580 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Ser Ala Val Trp Cys Leu Asn Gly Phe Thr Gly Arg His Arg His Gly
1 5 10 15

Arg Cys Arg Val Arg Ala Ser Gly Trp Arg Ser Ser Asn Arg Trp Cys
20 25 30

Ser Thr Thr Ala Asp Cys Cys Ala Ser Lys Thr Pro Thr Gln Ala Ala
35 40 45

Ser Pro Leu Glu Arg Arg Phe Thr Cys Cys Ser Pro Ala Val Gly Cys
50 55 60

Arg Phe Arg Ser Phe Pro Val Arg Arg Leu Ala Leu Gly Ala Arg Thr
65 70 75 80

Ser Arg Thr Leu Gly Val Arg Arg Thr Leu Ser Gln Trp Asn Leu Ser
85 90 95

Pro Arg Ala Gln Pro Ser Cys Ala Val Thr Val Glu Ser His Thr His
100 105 110

Ala Ser Pro Arg Met Ala Lys Leu Ala Arg Val Val Gly Leu Val Gln
115 120 125

Glu Glu Gln Pro Ser Asp Met Thr Asn His Pro Arg Tyr Ser Pro Pro
130 135 140

Pro Gln Gln Pro Gly Thr Pro Gly Tyr Ala Gln Gly Gln Gln Gln Thr
145 150 155 160

Tyr Ser Gln Gln Phe Asp Trp Arg Tyr Pro Pro Ser Pro Pro Pro Gln
165 170 175

Pro Thr Gln Tyr Arg Gln Pro Tyr Glu Ala Leu Gly Gly Thr Arg Pro
180 185 190

Gly Leu Ile Pro Gly Val Ile Pro Thr Met Thr Pro Pro Pro Gly Met
195 200 205

110

Val Arg Gln Arg Pro Arg Ala Gly Met Leu Ala Ile Gly Ala Val Thr
210 215 220

Ile Ala Val Val Ser Ala Gly Ile Gly Gly Ala Ala Ala Ser Leu Val
225 230 235 240

Gly Phe Asn Arg Ala Pro Ala Gly Pro Ser Gly Gly Pro Val Ala Ala
245 250 255

Ser Ala Ala Pro Ser Ile Pro Ala Ala Asn Met Pro Pro Gly Ser Val
260 265 270

Glu Gln Val Ala Ala Lys Val Val Pro Ser Val Val Met Leu Glu Thr
275 280 285

Asp Leu Gly Arg Gln Ser Glu Glu Gly Ser Gly Ile Ile Leu Ser Ala
290 295 300

Glu Gly Leu Ile Leu Thr Asn Asn His Val Ile Ala Ala Ala Ala Lys
305 310 315 320

Pro Pro Leu Gly Ser Pro Pro Pro Lys Thr Thr Val Thr Phe Ser Asp
325 330 335

Gly Arg Thr Ala Pro Phe Thr Val Val Gly Ala Asp Pro Thr Ser Asp
340 345 350

Ile Ala Val Val Arg Val Gln Gly Val Ser Gly Leu Thr Pro Ile Ser
355 360 365

Leu Gly Ser Ser Ser Asp Leu Arg Val Gly Gln Pro Val Leu Ala Ile
370 375 380

Gly Ser Pro Leu Gly Leu Glu Gly Thr Val Thr Thr Gly Ile Val Ser
385 390 395 400

Ala Leu Asn Arg Pro Val Ser Thr Thr Gly Glu Ala Gly Asn Gln Asn
405 410 415

Thr Val Leu Asp Ala Ile Gln Thr Asp Ala Ala Ile Asn Pro Gly Asn
420 425 430

Ser Gly Gly Ala Leu Val Asn Met Asn Ala Gln Leu Val Gly Val Asn
435 440 445

Ser Ala Ile Ala Thr Leu Gly Ala Asp Ser Ala Asp Ala Gln Ser Gly
450 455 460

Ser Ile Gly Leu Gly Phe Ala Ile Pro Val Asp Gln Ala Lys Arg Ile
465 470 475 480

Ala Asp Glu Leu Ile Ser Thr Gly Lys Ala Ser His Ala Ser Leu Gly
485 490 495

Val Gln Val Thr Asn Asp Lys Asp Thr Pro Gly Ala Lys Ile Val Glu
500 505 510

Val Val Ala Gly Gly Ala Ala Asn Ala Gly Val Pro Lys Gly Val
515 520 525

Val Val Thr Lys Val Asp Asp Arg Pro Ile Asn Ser Ala Asp Ala Leu
530 535 540

Val Ala Ala Val Arg Ser Lys Ala Pro Gly Ala Thr Val Ala Leu Thr
545 550 555 560

Phe Gln Asp Pro Ser Gly Gly Ser Arg Thr Val Gln Val Thr Leu Gly
565 570 575

Lys Ala Glu Gln
580

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 233 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Met Asn Asp Gly Lys Arg Ala Val Thr Ser Ala Val Leu Val Val Leu
1 5 10 15

112

Gly Ala Cys Leu Ala Leu Trp Leu Ser Gly Cys Ser Ser Pro Lys Pro
20 25 30

Asp Ala Glu Glu Gln Gly Val Pro Val Ser Pro Thr Ala Ser Asp Pro
35 40 45

Ala Leu Leu Ala Glu Ile Arg Gln Ser Leu Asp Ala Thr Lys Gly Leu
50 55 60

Thr Ser Val His Val Ala Val Arg Thr Thr Gly Lys Val Asp Ser Leu
65 70 75 80

Leu Gly Ile Thr Ser Ala Asp Val Asp Val Arg Ala Asn Pro Leu Ala
85 90 95

Ala Lys Gly Val Cys Thr Tyr Asn Asp Glu Gln Gly Val Pro Phe Arg
100 105 110

Val Gln Gly Asp Asn Ile Ser Val Lys Leu Phe Asp Asp Trp Ser Asn
115 120 125

Leu Gly Ser Ile Ser Glu Leu Ser Thr Ser Arg Val Leu Asp Pro Ala
130 135 140

Ala Gly Val Thr Gln Leu Leu Ser Gly Val Thr Asn Leu Gln Ala Gln
145 150 155 160

Gly Thr Glu Val Ile Asp Gly Ile Ser Thr Thr Lys Ile Thr Gly Thr
165 170 175

Ile Pro Ala Ser Ser Val Lys Met Leu Asp Pro Gly Ala Lys Ser Ala
180 185 190

Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser His His Leu Val
195 200 205

Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln Leu Thr Gln Ser
210 215 220

Lys Trp Asn Glu Pro Val Asn Val Asp
225 230

(2) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 66 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Val Ile Asp Ile Ile Gly Thr Ser Pro Thr Ser Trp Glu Gln Ala Ala
1 5 10 15

Ala Glu Ala Val Gln Arg Ala Arg Asp Ser Val Asp Asp Ile Arg Val
20 25 30

Ala Arg Val Ile Glu Gln Asp Met Ala Val Asp Ser Ala Gly Lys Ile
35 40 45

Thr Tyr Arg Ile Lys Leu Glu Val Ser Phe Lys Met Arg Pro Ala Gln
50 55 60

Pro Arg
65

(2) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 69 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Val Pro Pro Ala Pro Pro Leu Pro Pro Leu Pro Pro Ser Pro Ile Ser
1 5 10 15

Cys Ala Ser Pro Pro Ser Pro Pro Leu Pro Pro Ala Pro Pro Val Ala
20 25 30

Pro Gly Pro Pro Met Pro Pro Leu Asp Pro Trp Pro Pro Ala Pro Pro
35 40 45

Leu Pro Tyr Ser Thr Pro Pro Gly Ala Pro Leu Pro Pro Ser Pro Pro
50 55 60

Ser Pro Pro Leu Pro
65

(2) INFORMATION FOR SEQ ID NO:79:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 355 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Met Ser Asn Ser Arg Arg Arg Ser Leu Arg Trp Ser Trp Leu Leu Ser
1 5 10 15

Val Leu Ala Ala Val Gly Leu Gly Leu Ala Thr Ala Pro Ala Gln Ala
20 25 30

Ala Pro Pro Ala Leu Ser Gln Asp Arg Phe Ala Asp Phe Pro Ala Leu
35 40 45

Pro Leu Asp Pro Ser Ala Met Val Ala Gln Val Ala Pro Gln Val Val
50 55 60

Asn Ile Asn Thr Lys Leu Gly Tyr Asn Asn Ala Val Gly Ala Gly Thr
65 70 75 80

Gly Ile Val Ile Asp Pro Asn Gly Val Val Leu Thr Asn Asn His Val
85 90 95

Ile Ala Gly Ala Thr Asp Ile Asn Ala Phe Ser Val Gly Ser Gly Gln
100 105 110

Thr Tyr Gly Val Asp Val Val Gly Tyr Asp Arg Thr Gln Asp Val Ala
115 120 125

Val Leu Gln Leu Arg Gly Ala Gly Gly Leu Pro Ser Ala Ala Ile Gly
130 135 140

Gly Gly Val Ala Val Gly Glu Pro Val Val Ala Met Gly Asn Ser Gly
145 150 155 160

Gly Gln Gly Gly Thr Pro Arg Ala Val Pro Gly Arg Val Val Ala Leu
165 170 175

Gly Gln Thr Val Gln Ala Ser Asp Ser Leu Thr Gly Ala Glu Glu Thr
180 185 190

Leu Asn Gly Leu Ile Gln Phe Asp Ala Ala Ile Gln Pro Gly Asp Ser
195 200 205

Gly Gly Pro Val Val Asn Gly Leu Gly Gln Val Val Gly Met Asn Thr
210 215 220

Ala Ala Ser Asp Asn Phe Gln Leu Ser Gln Gly Gln Gly Phe Ala
225 230 235 240

Ile Pro Ile Gly Gln Ala Met Ala Ile Ala Gly Gln Ile Arg Ser Gly
245 250 255

Gly Gly Ser Pro Thr Val His Ile Gly Pro Thr Ala Phe Leu Gly Leu
260 265 270

Gly Val Val Asp Asn Asn Gly Asn Gly Ala Arg Val Gln Arg Val Val
275 280 285

Gly Ser Ala Pro Ala Ala Ser Leu Gly Ile Ser Thr Gly Asp Val Ile
290 295 300

Thr Ala Val Asp Gly Ala Pro Ile Asn Ser Ala Thr Ala Met Ala Asp
305 310 315 320

Ala Leu Asn Gly His His Pro Gly Asp Val Ile Ser Val Asn Trp Gln
325 330 335

Thr Lys Ser Gly Gly Thr Arg Thr Gly Asn Val Thr Leu Ala Glu Gly
340 345 350

Pro Pro Ala
355

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 205 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

Ser Pro Lys Pro Asp Ala Glu Glu Gln Gly Val Pro Val Ser Pro Thr
1 5 10 15

Ala Ser Asp Pro Ala Leu Leu Ala Glu Ile Arg Gln Ser Leu Asp Ala
20 25 30

Thr Lys Gly Leu Thr Ser Val His Val Ala Val Arg Thr Thr Gly Lys
35 40 45

Val Asp Ser Leu Leu Gly Ile Thr Ser Ala Asp Val Asp Val Arg Ala
50 55 60

Asn Pro Leu Ala Ala Lys Gly Val Cys Thr Tyr Asn Asp Glu Gln Gly
65 70 75 80

Val Pro Phe Arg Val Gln Gly Asp Asn Ile Ser Val Lys Leu Phe Asp
85 90 95

Asp Trp Ser Asn Leu Gly Ser Ile Ser Glu Leu Ser Thr Ser Arg Val
100 105 110

Leu Asp Pro Ala Ala Gly Val Thr Gln Leu Leu Ser Gly Val Thr Asn
115 120 125

Leu Gln Ala Gln Gly Thr Glu Val Ile Asp Gly Ile Ser Thr Thr Lys
130 135 140

Ile Thr Gly Thr Ile Pro Ala Ser Ser Val Lys Met Leu Asp Pro Gly

117

145	150	155	160
Ala Lys Ser Ala Arg Pro Ala Thr Val Trp Ile Ala Gln Asp Gly Ser			
165	170	175	
His His Leu Val Arg Ala Ser Ile Asp Leu Gly Ser Gly Ser Ile Gln			
180	185	190	
Leu Thr Gln Ser Lys Trp Asn Glu Pro Val Asn Val Asp			
195	200	205	

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 286 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

Gly Asp Ser Phe Trp Ala Ala Ala Asp Gln Met Ala Arg Gly Phe Val			
1	5	10	15
Leu Gly Ala Thr Ala Gly Arg Thr Thr Leu Thr Gly Glu Gly Leu Gln			
20	25	30	
His Ala Asp Gly His Ser Leu Leu Leu Asp Ala Thr Asn Pro Ala Val			
35	40	45	
Val Ala Tyr Asp Pro Ala Phe Ala Tyr Glu Ile Gly Tyr Ile Xaa Glu			
50	55	60	
Ser Gly Leu Ala Arg Met Cys Gly Glu Asn Pro Glu Asn Ile Phe Phe			
65	70	75	80
Tyr Ile Thr Val Tyr Asn Glu Pro Tyr Val Gln Pro Pro Glu Pro Glu			
85	90	95	
Asn Phe Asp Pro Glu Gly Val Leu Gly Gly Ile Tyr Arg Tyr His Ala			
100	105	110	

Ala Thr Glu Gln Arg Thr Asn Lys Xaa Gln Ile Leu Ala Ser Gly Val
115 120 125

Ala Met Pro Ala Ala Leu Arg Ala Ala Gln Met Leu Ala Ala Glu Trp
130 135 140

Asp Val Ala Ala Asp Val Trp Ser Val Thr Ser Trp Gly Glu Leu Asn
145 150 155 160

Arg Asp Gly Val Val Ile Glu Thr Glu Lys Leu Arg His Pro Asp Arg
165 170 175

Pro Ala Gly Val Pro Tyr Val Thr Arg Ala Leu Glu Asn Ala Arg Gly
180 185 190

Pro Val Ile Ala Val Ser Asp Trp Met Arg Ala Val Pro Glu Gln Ile
195 200 205

Arg Pro Trp Val Pro Gly Thr Tyr Leu Thr Leu Gly Thr Asp Gly Phe
210 215 220

Gly Phe Ser Asp Thr Arg Pro Ala Gly Arg Arg Tyr Phe Asn Thr Asp
225 230 235 240

Ala Glu Ser Gln Val Gly Arg Gly Phe Gly Arg Gly Trp Pro Gly Arg
245 250 255

Arg Val Asn Ile Asp Pro Phe Gly Ala Gly Arg Gly Pro Pro Ala Gln
260 265 270

Leu Pro Gly Phe Asp Glu Gly Gly Leu Arg Pro Xaa Lys
275 280 285

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 173 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Thr Lys Phe His Ala Leu Met Gln Glu Gln Ile His Asn Glu Phe Thr
1 5 10 15

Ala Ala Gln Gln Tyr Val Ala Ile Ala Val Tyr Phe Asp Ser Glu Asp
20 25 30

Leu Pro Gln Leu Ala Lys His Phe Tyr Ser Gln Ala Val Glu Glu Arg
35 40 45

Asn His Ala Met Met Leu Val Gln His Leu Leu Asp Arg Asp Leu Arg
50 55 60

Val Glu Ile Pro Gly Val Asp Thr Val Arg Asn Gln Phe Asp Arg Pro
65 70 75 80

Arg Glu Ala Leu Ala Leu Asp Gln Glu Arg Thr Val Thr Asp
85 90 95

Gln Val Gly Arg Leu Thr Ala Val Ala Arg Asp Glu Gly Asp Phe Leu
100 105 110

Gly Glu Gln Phe Met Gln Trp Phe Leu Gln Glu Gln Ile Glu Glu Val
115 120 125

Ala Leu Met Ala Thr Leu Val Arg Val Ala Asp Arg Ala Gly Ala Asn
130 135 140

Leu Phe Glu Leu Glu Asn Phe Val Ala Arg Glu Val Asp Val Ala Pro
145 150 155 160

Ala Ala Ser Gly Ala Pro His Ala Ala Gly Gly Arg Leu
165 170

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 107 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

120

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

Arg Ala Asp Glu Arg Lys Asn Thr Thr Met Lys Met Val Lys Ser Ile
1 5 10 15

Ala Ala Gly Leu Thr Ala Ala Ala Ala Ile Gly Ala Ala Ala Ala Gly
20 25 30

Val Thr Ser Ile Met Ala Gly Gly Pro Val Val Tyr Gln Met Gln Pro
35 40 45

Val Val Phe Gly Ala Pro Leu Pro Leu Asp Pro Xaa Ser Ala Pro Xaa
50 55 60

Val Pro Thr Ala Ala Gln Trp Thr Xaa Leu Leu Asn Xaa Leu Xaa Asp
65 70 75 80

Pro Asn Val Ser Phe Xaa Asn Lys Gly Ser Leu Val Glu Gly Gly Ile
85 90 95

Gly Gly Xaa Glu Gly Xaa Xaa Arg Arg Xaa Gln
100 105

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 125 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

Val Leu Ser Val Pro Val Gly Asp Gly Phe Trp Xaa Arg Val Val Asn
1 5 10 15

Pro Leu Gly Gln Pro Ile Asp Gly Arg Gly Asp Val Asp Ser Asp Thr
20 25 30

121

Arg Arg Ala Leu Glu Leu Gln Ala Pro Ser Val Val Xaa Arg Gln Gly
35 40 45

Val Lys Glu Pro Leu Xaa Thr Gly Ile Lys Ala Ile Asp Ala Met Thr
50 55 60

Pro Ile Gly Arg Gly Gln Arg Gln Leu Ile Ile Gly Asp Arg Lys Thr
65 70 75 80

Gly Lys Asn Arg Arg Leu Cys Arg Thr Pro Ser Ser Asn Gln Arg Glu
85 90 95

Glu Leu Gly Val Arg Trp Ile Pro Arg Ser Arg Cys Ala Cys Val Tyr
100 105 110

Val Gly His Arg Ala Arg Arg Gly Thr Tyr His Arg Arg
115 120 125

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 117 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

Cys Asp Ala Val Met Gly Phe Leu Gly Gly Ala Gly Pro Leu Ala Val
1 5 10 15

Val Asp Gln Gln Leu Val Thr Arg Val Pro Gln Gly Trp Ser Phe Ala
20 25 30

Gln Ala Ala Ala Val Pro Val Val Phe Leu Thr Ala Trp Tyr Gly Leu
35 40 45

Ala Asp Leu Ala Glu Ile Lys Ala Gly Glu Ser Val Leu Ile His Ala
50 55 60

Gly Thr Gly Gly Val Gly Met Ala Ala Val Gln Leu Ala Arg Gln Trp

122

65 70 75 80
Gly Val Glu Val Phe Val Thr Ala Ser Arg Gly Lys Trp Asp Thr Leu
 85 90 95
Arg Ala Xaa Xaa Phe Asp Asp Xaa Pro Tyr Arg Xaa Phe Pro His Xaa
 100 105 110
Arg Ser Ser Xaa Gly
 115

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 103 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

Met Tyr Arg Phe Ala Cys Arg Thr Leu Met Leu Ala Ala Cys Ile Leu
1 5 10 15
Ala Thr Gly Val Ala Gly Leu Gly Val Gly Ala Gln Ser Ala Ala Gln
20 25 30
Thr Ala Pro Val Pro Asp Tyr Tyr Trp Cys Pro Gly Gln Pro Phe Asp
35 40 45
Pro Ala Trp Gly Pro Asn Trp Asp Pro Tyr Thr Cys His Asp Asp Phe
50 55 60
His Arg Asp Ser Asp Gly Pro Asp His Ser Arg Asp Tyr Pro Gly Pro
65 70 75 80
Ile Leu Glu Gly Pro Val Leu Asp Asp Pro Gly Ala Ala Pro Pro Pro
85 90 95
Pro Ala Ala Gly Gly Gly Ala
100

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 88 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

Val Gln Cys Arg Val Trp Leu Glu Ile Gln Trp Arg Gly Met Leu Gly
1 5 10 15

Ala Asp Gln Ala Arg Ala Gly Gly Pro Ala Arg Ile Trp Arg Glu His
20 25 30

Ser Met Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala
35 40 45

Thr Lys Glu Gly Arg Gly Ile Val Met Arg Val Pro Leu Glu Gly Gly
50 55 60

Gly Arg Leu Val Val Glu Leu Thr Pro Asp Glu Ala Ala Leu Gly
65 70 75 80

Asp Glu Leu Lys Gly Val Thr Ser
85

(2) INFORMATION FOR SEQ ID NO:88:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 95 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

124

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

Thr Asp Ala Ala Thr Leu Ala Gln Glu Ala Gly Asn Phe Glu Arg Ile
1 5 10 15

Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala Gly
20 25 30

Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln Ala
35 40 45

Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu Leu
50 55 60

Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg
65 70 75 80

Ala Asp Glu Glu Gln Gln Ala Leu Ser Ser Gln Met Gly Phe
85 90 95

(2) INFORMATION FOR SEQ ID NO:89:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 166 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

Met Thr Gln Ser Gln Thr Val Thr Val Asp Gln Gln Glu Ile Leu Asn
1 5 10 15

Arg Ala Asn Glu Val Glu Ala Pro Met Ala Asp Pro Pro Thr Asp Val
20 25 30

Pro Ile Thr Pro Cys Glu Leu Thr Xaa Xaa Lys Asn Ala Ala Gln Gln
35 40 45

Xaa Val Leu Ser Ala Asp Asn Met Arg Glu Tyr Leu Ala Ala Gly Ala
50 55 60

125

Lys Glu Arg Gln Arg Leu Ala Thr Ser Leu Arg Asn Ala Ala Lys Xaa
65 70 75 80

Tyr Gly Glu Val Asp Glu Glu Ala Ala Thr Ala Leu Asp Asn Asp Gly
85 90 95

Glu Gly Thr Val Gln Ala Glu Ser Ala Gly Ala Val Gly Gly Asp Ser
100 105 110

Ser Ala Glu Leu Thr Asp Thr Pro Arg Val Ala Thr Ala Gly Glu Pro
115 120 125

Asn Phe Met Asp Leu Lys Glu Ala Ala Arg Lys Leu Glu Thr Gly Asp
130 135 140

Gln Gly Ala Ser Leu Ala His Xaa Gly Asp Gly Trp Asn Thr Xaa Thr
145 150 155 160

Leu Thr Leu Gln Gly Asp
165

(2) INFORMATION FOR SEQ ID NO:90:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 5 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

Arg Ala Glu Arg Met
1 5

(2) INFORMATION FOR SEQ ID NO:91:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 263 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single

126

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Val	Ala	Trp	Met	Ser	Val	Thr	Ala	Gly	Gln	Ala	Glu	Leu	Thr	Ala	Ala
1					5					10					15
Gln	Val	Arg	Val	Ala	Ala	Ala	Tyr	Glu	Thr	Ala	Tyr	Gly	Leu	Thr	
			20					25				30			
Val	Pro	Pro	Pro	Val	Ile	Ala	Glu	Asn	Arg	Ala	Glu	Leu	Met	Ile	Leu
					35			40					45		
Ile	Ala	Thr	Asn	Leu	Leu	Gly	Gln	Asn	Thr	Pro	Ala	Ile	Ala	Val	Asn
				50			55				60				
Glu	Ala	Glu	Tyr	Gly	Glu	Met	Trp	Ala	Gln	Asp	Ala	Ala	Ala	Met	Phe
					65		70			75				80	
Gly	Tyr	Ala	Ala	Ala	Thr	Ala	Thr	Ala	Thr	Ala	Thr	Leu	Leu	Pro	Phe
					85			90				95			
Glu	Glu	Ala	Pro	Glu	Met	Thr	Ser	Ala	Gly	Gly	Leu	Leu	Glu	Gln	Ala
					100			105					110		
Ala	Ala	Val	Glu	Glu	Ala	Ser	Asp	Thr	Ala	Ala	Ala	Asn	Gln	Leu	Met
					115			120				125			
Asn	Asn	Val	Pro	Gln	Ala	Leu	Lys	Gln	Leu	Ala	Gln	Pro	Thr	Gln	Gly
					130		135				140				
Thr	Thr	Pro	Ser	Ser	Lys	Leu	Gly	Gly	Leu	Trp	Lys	Thr	Val	Ser	Pro
					145		150				155			160	
His	Arg	Ser	Pro	Ile	Ser	Asn	Met	Val	Ser	Met	Ala	Asn	Asn	His	Met
					165			170				175			
Ser	Met	Thr	Asn	Ser	Gly	Val	Ser	Met	Thr	Asn	Thr	Leu	Ser	Ser	Met
					180			185				190			
Leu	Lys	Gly	Phe	Ala	Pro	Ala	Ala	Ala	Gln	Ala	Val	Gln	Thr	Ala	

127

195

200

205

Ala Gln Asn Gly Val Arg Ala Met Ser Ser Leu Gly Ser Ser Leu Gly
210 215 220

Ser Ser Gly Leu Gly Gly Val Ala Ala Asn Leu Gly Arg Ala Ala
225 230 235 240

Ser Val Arg Tyr Gly His Arg Asp Gly Gly Lys Tyr Ala Xaa Ser Gly
245 250 255

Arg Arg Asn Gly Gly Pro Ala
260

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 303 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

Met Thr Tyr Ser Pro Gly Asn Pro Gly Tyr Pro Gln Ala Gln Pro Ala
1 5 10 15

Gly Ser Tyr Gly Gly Val Thr Pro Ser Phe Ala His Ala Asp Glu Gly
20 25 30

Ala Ser Lys Leu Pro Met Tyr Leu Asn Ile Ala Val Ala Val Leu Gly
35 40 45

Leu Ala Ala Tyr Phe Ala Ser Phe Gly Pro Met Phe Thr Leu Ser Thr
50 55 60

Glu Leu Gly Gly Asp Gly Ala Val Ser Gly Asp Thr Gly Leu Pro
65 70 75 80

Val Gly Val Ala Leu Leu Ala Ala Leu Leu Ala Gly Val Val Leu Val
85 90 95

Pro Lys Ala Lys Ser His Val Thr Val Val Ala Val Leu Gly Val Leu
100 105 110

Gly Val Phe Leu Met Val Ser Ala Thr Phe Asn Lys Pro Ser Ala Tyr
115 120 125

Ser Thr Gly Trp Ala Leu Trp Val Val Leu Ala Phe Ile Val Phe Gln
130 135 140

Ala Val Ala Ala Val Leu Ala Leu Leu Val Glu Thr Gly Ala Ile Thr
145 150 155 160

Ala Pro Ala Pro Arg Pro Lys Phe Asp Pro Tyr Gly Gln Tyr Gly Arg
165 170 175

Tyr Gly Gln Tyr Gly Gln Tyr Gly Val Gln Pro Gly Gly Tyr Tyr Gly
180 185 190

Gln Gln Gly Ala Gln Gln Ala Ala Gly Leu Gln Ser Pro Gly Pro Gln
195 200 205

Gln Ser Pro Gln Pro Pro Gly Tyr Gly Ser Gln Tyr Gly Gly Tyr Ser
210 215 220

Ser Ser Pro Ser Gln Ser Gly Ser Gly Tyr Thr Ala Gln Pro Pro Ala
225 230 235 240

Gln Pro Pro Ala Gln Ser Gly Ser Gln Gln Ser His Gln Gly Pro Ser
245 250 255

Thr Pro Pro Thr Gly Phe Pro Ser Phe Ser Pro Pro Pro Pro Val Ser
260 265 270

Ala Gly Thr Gly Ser Gln Ala Gly Ser Ala Pro Val Asn Tyr Ser Asn
275 280 285

Pro Ser Gly Gly Glu Gln Ser Ser Ser Pro Gly Gly Ala Pro Val
290 295 300

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 amino acids
- (B) TYPE: amino acid

129

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

Gly Cys Gly Glu Thr Asp Ala Ala Thr Leu Ala Gln Glu Ala Gly Asn
1 5 10 15

Phe Glu Arg Ile Ser Gly Asp Leu Lys Thr Gln Ile
20 25

(2) INFORMATION FOR SEQ ID NO:94:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 16 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

Asp Gln Val Glu Ser Thr Ala Gly Ser Leu Gln Gly Gln Trp Arg Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:95:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 27 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

130

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

Gly Cys Gly Ser Thr Ala Gly Ser Leu Gln Gly Gln Trp Arg Gly Ala
1 5 10 15
Ala Gly Thr Ala Ala Gln Ala Ala Val Val Arg
20 25

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

Gly Cys Gly Gly Thr Ala Ala Gln Ala Ala Val Val Arg Phe Gln Glu
 1 5 10 15
 Ala Ala Asn Lys Gln Lys Gln Glu Leu Asp Glu
 20 25

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

Gly Cys Gly Ala Asn Lys Gln Lys Gln Glu Leu Asp Glu Ile Ser Thr
1 5 10 15

Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg
20 25

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

Gly Cys Gly Ile Arg Gln Ala Gly Val Gln Tyr Ser Arg Ala Asp Glu
1 5 10 15

Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe
20 25

(2) INFORMATION FOR SEQ ID NO:99:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 507 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

ATGAAGATGG TGAAATCGAT CGCCGCAGGT CTGACCGCCG CGGCTGCAAT CGGCGCCGCT	60
CGGGCCGGTG TGACTTCGAT CATGGCTGGC GGCCCGGTG TATACCAGAT GCAGCCGGTC	120
GTCTTCGGCG CGCCACTGCC GTTGGACCCG GCATCCGCC CTGACGTCCC GACCGCCGCC	180
CAGTTGACCA GCCTGCTCAA CAGCCTCGCC GATCCCAACG TGTCGTTGC GAACAAGGGC	240

AGTCTGGTCG AGGGCGGCAT CGGGGGCACC GAGGCGCGCA TCGCCGACCA CAAGCTGAAG	300
AAGGCCGCCG AGCACGGGGA TCTGCCGCTG TCGTTCAGCG TGACGAACAT CCAGCCGGCG	360
GCCGCCGGTT CGGCCACCGC CGACGTTCC GTCTGGGTC CGAAGCTCTC GTCGCCGGTC	420
ACGCAGAACG TCACGTTCGT GAATCAAGGC GGCTGGATGC TGTCACGCCGC ATCGGCGATG	480
GAGTTGCTGC AGGCCGCAGG GAACTGA	507

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 168 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

Met Lys Met Val Lys Ser Ile Ala Ala Gly Leu Thr Ala Ala Ala Ala			
1	5	10	15
Ile Gly Ala Ala Ala Gly Val Thr Ser Ile Met Ala Gly Gly Pro			
20	25	30	
Val Val Tyr Gln Met Gln Pro Val Val Phe Gly Ala Pro Leu Pro Leu			
35	40	45	
Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln Leu Thr Ser			
50	55	60	
Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala Asn Lys Gly			
65	70	75	80
Ser Leu Val Glu Gly Gly Ile Gly Gly Thr Glu Ala Arg Ile Ala Asp			
85	90	95	
His Lys Leu Lys Lys Ala Ala Glu His Gly Asp Leu Pro Leu Ser Phe			
100	105	110	

Ser Val Thr Asn Ile Gln Pro Ala Ala Ala Gly Ser Ala Thr Ala Asp
 115 120 125

Val Ser Val Ser Gly Pro Lys Leu Ser Ser Pro Val Thr Gln Asn Val
 130 135 140

Thr Phe Val Asn Gln Gly Gly Trp Met Leu Ser Arg Ala Ser Ala Met
 145 150 155 160

Glu Leu Leu Gln Ala Ala Gly Asn
 165

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS.

- SEQUENCE CHARACTERISTICS:

 - (A) LENGTH: 500 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

CGTGGCAATG TCGTTGACCG TCGGGGCCGG GGTCGCCTCC GCAGATCCCCG TGGACGCGGT 60
CATTAACACC ACCTGCAATT ACGGGCAGGT AGTAGCTGCG CTCAACGCGA CGGATCCGGG 120
GGCTGCCGCA CAGTTCAACG CCTCACCGGT GGCGCAGTCC TATTGCGCA ATTTCCTCGC 180
CGCACCGCCA CCTCAGCGCG CTGCCATGGC CGCGCAATTG CAAGCTGTGC CGGGGGCGGC 240
ACAGTACATC GCCCTTGTG 420 AGTCGGTTGC CGGCTCCTGC AACAACTATT AAGCCCATGC 300
GGGCCCCATC CCGCGACCCG GCATCGTCGC CGGGGCTAGG CCAGATTGCC CCGCTCCTCA 360
ACGGGCGCGA TCCCGCGACC CGGCATCGTC GCCGGGGCTA GGCCAGATTG CCCCCTCC 420
CAACGGGCCG CATCTCGTGC CGAATTCTG CAGCCCCGGG GATCCACTAG TTCTAGAGCG 480
GCCGCCACCG CGGTGGAGCT 500

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 96 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

Val Ala Met Ser Leu Thr Val Gly Ala Gly Val Ala Ser Ala Asp Pro
1 5 10 15

Val Asp Ala Val Ile Asn Thr Thr Cys Asn Tyr Gly Gln Val Val Ala
20 25 30

Ala Leu Asn Ala Thr Asp Pro Gly Ala Ala Ala Gln Phe Asn Ala Ser
35 40 45

Pro Val Ala Gln Ser Tyr Leu Arg Asn Phe Leu Ala Ala Pro Pro Pro
50 55 60

Gln Arg Ala Ala Met Ala Ala Gln Leu Gln Ala Val Pro Gly Ala Ala
65 70 75 80

Gln Tyr Ile Gly Leu Val Glu Ser Val Ala Gly Ser Cys Asn Asn Tyr
85 90 95

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 154 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

ATGACAGAGC AGCAGTGGAA TTTCGCGGGT ATCGAGGCCG CGGCAAGCGC AATCCAGGGA	60
AATGTCACGT CCATTCATTG CCTCCTTGAC GAGGGGAAGC AGTCCCTGAC CAAGCTCGCA	120
GC GGCCCTGGG GCGGTAGCGG TTCGGAAGCG TACC	154

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 51 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

Met Thr Glu Gln Gln Trp Asn Phe Ala Gly Ile Glu Ala Ala Ala Ser			
1	5	10	15
Ala Ile Gln Gly Asn Val Thr Ser Ile His Ser Leu Leu Asp Glu Gly			
20	25	30	
Lys Gln Ser Leu Thr Lys Leu Ala Ala Ala Trp Gly Gly Ser Gly Ser			
35	40	45	
Glu Ala Tyr			
50			

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 282 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

CGGTCGCGCA CTTCCAGGTG ACTATGAAAG TCGGCTTCCG NCTGGAGGAT TCCTGAACCT	60
TCAAGCGCGG CCGATAACTG AGGTGCATCA TTAAGCGACT TTTCCAGAAC ATCCTGACGC	120
GCTCGAAACG CGGCACAGCC GACGGTGGCT CCGNCGAGGC GCTGNCTCCA AAATCCCTGA	180
GACAATTCGN CGGGGGCGCC TACAAGGAAG TCGGTGCTGA ATTGNCGNG TATCTGGTCG	240
ACCTGTGTGG TCTGNAGCCG GACGAAGCGG TGCTCGACGT CG	282

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1565 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

GTATGCGGCC ACTGAAGTCG CCAATGCGGC GGCGGCCAGC TAAGCCAGGA ACAGTCGGCA	60
CGAGAAACCA CGAGAAATAG GGACACGTA TGGTGGATTG CGGGCGTTA CCACCGGAGA	120
TCAACTCCGC GAGGATGTAC GCCGGCCCGG GTTCGGCCTC GCTGGTGGCC GCGGCTCAGA	180
TGTGGGACAG CGTGGCGAGT GACCTGTTT CGGCCGCGTC GGCGTTTCAG TCGGTGGTCT	240
GGGGTCTGAC GGTGGGGTCG TGGATAGGTT CGTCGGCGGG TCTGATGGTG GCGGCGGCCT	300
CGCCGTATGT GGCGTGGATG AGCGTCACCG CGGGGCAGGC CGAGCTGACC GCCGCCAGG	360
TCCGGGTTGC TGCAGCGGCC TACGAGACGG CGTATGGCT GACGGTGCCTC CCGCCGGTGA	420
TCGCCGAGAA CCGTGCTGAA CTGATGATTG TGATAGCGAC CAACCTCTTG GGGCAAAACA	480
CCCCGGCGAT CGCGGTCAAC GAGGCCGAAT ACGGCGAGAT GTGGGCCAA GACGCCGCCG	540
CGATGTTGG CTACGCCGCG GCGACGGCGA CGGCGACGGC GACGTTGCTG CCGTTCGAGG	600

AGGCGCCCGA GATGACCAGC GCGGGTGGGC TCCTCGAGCA GGCCGCCGCG GTCGAGGAGG	660
CCTCCGACAC CGCCGCGGCG AACCAAGTTGA TGAACAATGT GCCCCAGGCG CTGCAACAGC	720
TGGCCCAGCC CACGCAGGGC ACCACGCCTT CTTCCAAGCT GGGTGGCCTG TGGAAGACGG	780
TCTCGCCGCA TCGGTGCGCG ATCAGCAACA TGGTGTCAAT GGCCAACAAC CACATGTCAA	840
TGACCAACTC GGGTGTGTCA ATGACCAACA CCTTGAGCTC GATGTTGAAG GGCTTGCTC	900
CGGCAGGGCGC CGCCCAGGCC GTGCAAACCG CGGCGCAAAA CGGGGTCCGG GCGATGAGCT	960
CGCTGGGCAG CTCGCTGGGT TCTTCGGTC TGGGCGGTGG GGTGGCCGCC AACTTGGTC	1020
GGGCAGGGCCTC GGTCGGTTCG TTGTCGGTGC CGCAGGCCTG GGCCGCGGCC AACCAGGCAG	1080
TCACCCCCGGC GGCGCGGGCG CTGCCGCTGA CCAGCCTGAC CAGCGCCGCG GAAAGAGGGC	1140
CCGGGCAGAT GCTGGGCGGG CTGCCGGTGG GGCAGATGGG CGCCAGGGCC GGTGGTGGGC	1200
TCAGTGGTGT GCTGCGTGT CCTATGTGAT GCCGCATTCT CCGCGGGCCG	1260
GCTAGGAGAG GGGGCGCAGA CTGTCGTTAT TTGACCAGTG ATCGGCGGTC TCGGTGTTTC	1320
CGCGGCCGGC TATGACAACA GTCAATGTGC ATGACAAGTT ACAGGTATTA GGTCCAGGTT	1380
CAACAAGGAG ACAGGCAACA TGGCCTCACG TTTTATGACG GATCCGCACG CGATGCGGGA	1440
CATGGCGGGC CGTTTGAAAG TGCACGCCA GACGGTGGAG GACGAGGCTC GCGGGATGTG	1500
GGCGTCCGCG CAAAACATTG CCGGTGCGGG CTGGAGTGGC ATGGCCGAGG CGACCTCGCT	1560
AGACA	1565

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 391 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

Met Val Asp Phe Gly Ala Leu Pro Pro Glu Ile Asn Ser Ala Arg Met
1 5 10 15

Tyr Ala Gly Pro Gly Ser Ala Ser Leu Val Ala Ala Ala Gln Met Trp
20 25 30

Asp Ser Val Ala Ser Asp Leu Phe Ser Ala Ala Ser Ala Phe Gln Ser
35 40 45

Val Val Trp Gly Leu Thr Val Gly Ser Trp Ile Gly Ser Ser Ala Gly
50 55 60

Leu Met Val Ala Ala Ala Ser Pro Tyr Val Ala Trp Met Ser Val Thr
65 70 75 80

Ala Gly Gln Ala Glu Leu Thr Ala Ala Gln Val Arg Val Ala Ala Ala
85 90 95

Ala Tyr Glu Thr Ala Tyr Gly Leu Thr Val Pro Pro Pro Val Ile Ala
100 105 110

Glu Asn Arg Ala Glu Leu Met Ile Leu Ile Ala Thr Asn Leu Leu Gly
115 120 125

Gln Asn Thr Pro Ala Ile Ala Val Asn Glu Ala Glu Tyr Gly Glu Met
130 135 140

Trp Ala Gln Asp Ala Ala Ala Met Phe Gly Tyr Ala Ala Ala Thr Ala
145 150 155 160

Thr Ala Thr Ala Thr Leu Leu Pro Phe Glu Glu Ala Pro Glu Met Thr
165 170 175

Ser Ala Gly Gly Leu Leu Glu Gln Ala Ala Ala Val Glu Glu Ala Ser
180 185 190

Asp Thr Ala Ala Ala Asn Gln Leu Met Asn Asn Val Pro Gln Ala Leu
195 200 205

Gln Gln Leu Ala Gln Pro Thr Gln Gly Thr Thr Pro Ser Ser Lys Leu
210 215 220

Gly Gly Leu Trp Lys Thr Val Ser Pro His Arg Ser Pro Ile Ser Asn
225 230 235 240

Met Val Ser Met Ala Asn Asn His Met Ser Met Thr Asn Ser Gly Val
245 250 255

Ser Met Thr Asn Thr Leu Ser Ser Met Leu Lys Gly Phe Ala Pro Ala
260 265 270

Ala Ala Ala Gln Ala Val Gln Thr Ala Ala Gln Asn Gly Val Arg Ala
275 280 285

Met Ser Ser Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Gly Gly
290 295 300

Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser Val
305 310 315 320

Pro Gln Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro Ala Ala Arg
325 330 335

Ala Leu Pro Leu Thr Ser Leu Thr Ser Ala Ala Glu Arg Gly Pro Gly
340 345 350

Gln Met Leu Gly Gly Leu Pro Val Gly Gln Met Gly Ala Arg Ala Gly
355 360 365

Gly Gly Leu Ser Gly Val Leu Arg Val Pro Pro Arg Pro Tyr Val Met
370 375 380

Pro His Ser Pro Ala Ala Gly
385 390

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 259 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

140

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

ACCAACACCT TGCACTCNAT GTTGAAGGGC TTAGCTCCGG CGGCGGCTCA GGCGTGAA	60
ACCGCGGCCG AAAACGGGGT CTGGGCAATG AGCTCGCTGG GCAGCCAGCT GGGTTCGTCG	120
CTGGGTTCTT CGGGTCTGGG CGCTGGGTG GCCGCCAACT TGGGTCGGGC GGCCCTCGGTC	180
GGTCGTTGT CGGTGCCGCC AGCATGGGCC GCGGCCAACC AGGCGGTCAC CCCGGCGGCG	240
CGGGCGCTGC CGCTGACCA	259

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 86 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

Thr Asn Thr Leu His Ser Met Leu Lys Gly Leu Ala Pro Ala Ala Ala			
1	5	10	15
Gln Ala Val Glu Thr Ala Ala Glu Asn Gly Val Trp Ala Met Ser Ser			
20	25	30	
Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu Gly Ala			
35	40	45	
Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser Leu Ser			
50	55	60	
Val Pro Pro Ala Trp Ala Ala Asn Gln Ala Val Thr Pro Ala Ala			
65	70	75	80
Arg Ala Leu Pro Leu Thr			
85			

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1109 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

TACTTGAGAG AATTTGACCT GTTGCCGACG TTGTTTGCCT GTCATCATTG GTGCTAGTTA	60
TGGCCGAGCG GAAGGATTAT CGAAGTGGTG GACTTCGGGG CGTTACCACC GGAGATCAAC	120
TCCGCGAGGA TGTACGCCGG CCCGGGTTCG GCCTCGCTGG TGGCCGCCGC GAAGATGTGG	180
GACAGCGTGG CGAGTGACCT GTTTTGGGCC GCGTCGGCGT TTCAGTCGGT GGTCTGGGT	240
CTGACGACGG GATCGTGGAT AGGTTCGTCG GCGGGTCTGA TGGTGGCGGC GGCTCGCCG	300
TATGTGGCGT GGATGAGCGT CACCGCGGGG CAGGCCGAGC TGACCGCCGC CCAGGTCCGG	360
GTTGCTGCCG CGGCCTACGA GACGGCGTAT GGGCTGACGG TGCCCCCGCC GGTGATGCC	420
GAGAACCGTG CTGAACGTGAT GATTCTGATA GCGACCAACC TCTTGGGGCA AAACACCCCG	480
GCGATCGCGG TCAACGAGGC CGAACATCGGG GAGATGTGGG CCCAAGACGC CGCCGCGATG	540
TTTGGCTACG CCGCCACGGC GGCGACGGCG ACCGAGGCCT TGCTGCCGTT CGAGGACGCC	600
CCACTGATCA CCAACCCCGG CGGGCTCCTT GAGCAGGCCG TCGCGGTCGA GGAGGCCATC	660
GACACCGCCG CGGCGAACCA GTTGATGAAC AATGTGCCCG AAGCGCTGCA ACAACTGGCC	720
CAGCCCCACGA AAAGCATCTG GCCGTTGAC CAACTGAGTG AACTCTGGAA AGCCATCTCG	780
CCGCATCTGT CGCCGCTCAG CAACATCGTG TCGATGCTCA ACAACCACGT GTCGATGACC	840
AACTCGGGTG TGTCAATGGC CAGCACCTTG CACTCAATGT TGAAGGGCTT TGCTCCGGCG	900
CGGGCTCAGG CGTGGAAAC CGCGCGCAA AACGGGGTCC AGGCGATGAG CTCGCTGGC	960

AGCCAGCTGG GTTCGTCGCT GGGTTCTTCG GGTCTGGCG CTGGGGTGGC CGCCAAC TTG 1020
GGTCGGGCGG CCTCGGTGCG TTCGTTGTCG GTGCCGCAGG CCTGGGCCGC GGCCAACCAG 1080
GCGGTCACCC CGGC GGCGCGCG GGCGCTGCC 1109

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 341 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Val Val Asp Phe Gly Ala Leu Pro Pro Glu Ile Asn Ser Ala Arg Met
1 5 10 15

Tyr Ala Gly Pro Gly Ser Ala Ser Leu Val Ala Ala Ala Lys Met Trp
20 25 30

Asp Ser Val Ala Ser Asp Leu Phe Ser Ala Ala Ser Ala Phe Gln Ser
35 40 45

Val Val Trp Gly Leu Thr Thr Gly Ser Trp Ile Gly Ser Ser Ala Gly
50 55 60

Leu Met Val Ala Ala Ala Ser Pro Tyr Val Ala Trp Met Ser Val Thr
65 70 75 80

Ala Gly Gln Ala Glu Leu Thr Ala Ala Gln Val Arg Val Ala Ala Ala
85 90 95

Ala Tyr Glu Thr Ala Tyr Gly Leu Thr Val Pro Pro Pro Val Ile Ala
100 105 110

Glu Asn Arg Ala Glu Leu Met Ile Leu Ile Ala Thr Asn Leu Leu Gly
115 120 125

143

Gln Asn Thr Pro Ala Ile Ala Val Asn Glu Ala Glu Tyr Gly Glu Met
 130 135 140
 Trp Ala Gln Asp Ala Ala Ala Met Phe Gly Tyr Ala Ala Thr Ala Ala
 145 150 155 160
 Thr Ala Thr Glu Ala Leu Leu Pro Phe Glu Asp Ala Pro Leu Ile Thr
 165 170 175
 Asn Pro Gly Gly Leu Leu Glu Gln Ala Val Ala Val Glu Glu Ala Ile
 180 185 190
 Asp Thr Ala Ala Ala Asn Gln Leu Met Asn Asn Val Pro Gln Ala Leu
 195 200 205
 Gln Gln Leu Ala Gln Pro Thr Lys Ser Ile Trp Pro Phe Asp Gln Leu
 210 215 220
 Ser Glu Leu Trp Lys Ala Ile Ser Pro His Leu Ser Pro Leu Ser Asn
 225 230 235 240
 Ile Val Ser Met Leu Asn Asn His Val Ser Met Thr Asn Ser Gly Val
 245 250 255
 Ser Met Ala Ser Thr Leu His Ser Met Leu Lys Gly Phe Ala Pro Ala
 260 265 270
 Ala Ala Gln Ala Val Glu Thr Ala Ala Gln Asn Gly Val Gln Ala Met
 275 280 285
 Ser Ser Leu Gly Ser Gln Leu Gly Ser Ser Leu Gly Ser Ser Gly Leu
 290 295 300
 Gly Ala Gly Val Ala Ala Asn Leu Gly Arg Ala Ala Ser Val Gly Ser
 305 310 315 320
 Leu Ser Val Pro Gln Ala Trp Ala Ala Ala Asn Gln Ala Val Thr Pro
 325 330 335
 Ala Ala Arg Ala Leu
 340

(2) INFORMATION FOR SEQ ID NO:112:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1256 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

CATCGGAGGG AGTGATCACC ATGCTGTGGC ACGCAATGCC ACCGGAGNTA AATACCGCAC	60
GGCTGATGGC CGGCAGCGGT CCGGCTCCAA TGCTTGCAGGC GGCCGCGGGA TGGCAGACGC	120
TTTCGGCGGC TCTGGACGCT CAGGCCGTG AGTTGACCGC GCGCCTGAAC TCTCTGGGAG	180
AAGCCTGGAC TGGAGGTGGC AGCGACAAGG CGCTTGCAGGC TGCAACGCCG ATGGTGGTCT	240
GGCTACAAAC CGCGTCAACA CAGGCCAAGA CCCGTGCGAT GCAGGGGACG GCGCAAGCCG	300
CGGCATACAC CCAGGCCATG GCCACGACGC CGTCGCTGCC GGAGATCGCC GCCAACACACA	360
TCACCCAGGC CGTCCTTACG GCCACCAACT TCTTCGGTAT CAACACGATC CCGATCGCGT	420
TGACCGAGAT GGATTATTTC ATCCGTATGT GGAACCAGGC AGCCCTGGCA ATGGAGGTCT	480
ACCAGGCCGA GACCGCGGTT AACACGCTTT TCGAGAAGCT CGAGCCGATG GCGTCGATCC	540
TTGATCCCGG CGCGAGCCAG AGCACGACGA ACCCGATCTT CGGAATGCC CCCCCCTGGCA	600
GCTAACACCC GGTTGGCCAG TTGCCGCCGG CGGCTACCCA GACCCTCGGC CAACTGGGTG	660
AGATGAGCGG CCCGATGCAG CAGCTGACCC AGCCGCTGCA GCAGGTGACG TCGTTGTTCA	720
GCCAGGTGGG CGGCACCGGC GGCGGCAACC CAGCCGACGA GGAAGCCGCG CAGATGGGCC	780
TGCTCGGCAC CAGTCCGCTG TCGAACCATC CGCTGGCTGG TGGATCAGGC CCCAGCGCGG	840
GCGCGGGCCT GCTGCGCGCG GAGTCGCTAC CTGGCGCAGG TGGGTCGTTG ACCCGCACGC	900
CGCTGATGTC TCAGCTGATC GAAAAGCCGG TTGCCCCCTC GGTGATGCCG GCGGCTGCTG	960
CCGGATCGTC GGCGACGGGT GGCGCCGCTC CGGTGGGTGC GGGAGCGATG GGCCAGGGTG	1020

CGCAATCCGG CGGCTCCACC AGGCCGGGTC TGGTCGCGCC GGCACCGCTC GCGCAGGAGC	1080
GTGAAGAAGA CGACGAGGAC GACTGGGACG AAGAGGACGA CTGGTGAGCT CCCGTAATGA	1140
CAACAGACTT CCGGCCACC CGGGCCGGAA GACTTGCAA CATTTGGCG AGGAAGGTAA	1200
AGAGAGAAAG TAGTCCAGCA TGGCAGAGAT GAAGACCGAT GCCGCTACCC TCGCGC	1256

(2) INFORMATION FOR SEQ ID NO:113:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 432 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

CTAGTGGATG GGACCATGGC CATTTCCTGC AGTCTCACTG CCTTCTGTGT TGACATTTG	60
GCACGCCGGC GGAAACGAAG CACTGGGTC GAAGAACGGC TGCGCTGCCA TATCGTCCGG	120
AGCTTCCATA CCTTCGTGCG GCCGGAAGAG CTTGTCGTAG TCGGCCGCCA TGACAACCTC	180
TCAGAGTGCCTCTAACACGTA TAAACACGAG AAAGGGCGAG ACCGACGGAA GGTCGAACCTC	240
GCCCCGATCCC GTGTTTCGCT ATTCTACGCG AACTCGGCGT TGCCCTATGC GAACATCCCA	300
GTGACGTTGC CTTCGGTGCA AGCCATTGCC TGACCGGCTT CGCTGATCGT CCGCGCCAGG	360
TTCTGCAGCG CGTTGTTCACTCGGTAGCC GTGGCGTCCC ATTTTGCTG GACACCCTGG	420
TACGCCCTCCG AA	432

(2) INFORMATION FOR SEQ ID NO:114:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 368 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

Met Leu Trp His Ala Met Pro Pro Glu Xaa Asn Thr Ala Arg Leu Met
1 5 10 15

Ala Gly Ala Gly Pro Ala Pro Met Leu Ala Ala Ala Ala Gly Trp Gln
20 25 30

Thr Leu Ser Ala Ala Leu Asp Ala Gln Ala Val Glu Leu Thr Ala Arg
35 40 45

Leu Asn Ser Leu Gly Glu Ala Trp Thr Gly Gly Ser Asp Lys Ala
50 55 60

Leu Ala Ala Ala Thr Pro Met Val Val Trp Leu Gln Thr Ala Ser Thr
65 70 75 80

Gln Ala Lys Thr Arg Ala Met Gln Ala Thr Ala Gln Ala Ala Tyr
85 90 95

Thr Gln Ala Met Ala Thr Thr Pro Ser Leu Pro Glu Ile Ala Ala Asn
100 105 110

His Ile Thr Gln Ala Val Leu Thr Ala Thr Asn Phe Phe Gly Ile Asn
115 120 125

Thr Ile Pro Ile Ala Leu Thr Glu Met Asp Tyr Phe Ile Arg Met Trp
130 135 140

Asn Gln Ala Ala Leu Ala Met Glu Val Tyr Gln Ala Glu Thr Ala Val
145 150 155 160

Asn Thr Leu Phe Glu Lys Leu Glu Pro Met Ala Ser Ile Leu Asp Pro
165 170 175

Gly Ala Ser Gln Ser Thr Thr Asn Pro Ile Phe Gly Met Pro Ser Pro
180 185 190

Gly Ser Ser Thr Pro Val Gly Gln Leu Pro Pro Ala Ala Thr Gln Thr
195 200 205

Leu Gly Gln Leu Gly Glu Met Ser Gly Pro Met Gln Gln Leu Thr Gln
210 215 220

Pro Leu Gln Gln Val Thr Ser Leu Phe Ser Gln Val Gly Gly Thr Gly
225 230 235 240

Gly Gly Asn Pro Ala Asp Glu Glu Ala Ala Gln Met Gly Leu Leu Gly
245 250 255

Thr Ser Pro Leu Ser Asn His Pro Leu Ala Gly Gly Ser Gly Pro Ser
260 265 270

Ala Gly Ala Gly Leu Leu Arg Ala Glu Ser Leu Pro Gly Ala Gly Gly
275 280 285

Ser Leu Thr Arg Thr Pro Leu Met Ser Gln Leu Ile Glu Lys Pro Val
290 295 300

Ala Pro Ser Val Met Pro Ala Ala Ala Gly Ser Ser Ala Thr Gly
305 310 315 320

Gly Ala Ala Pro Val Gly Ala Gly Ala Met Gly Gln Gly Ala Gln Ser
325 330 335

Gly Gly Ser Thr Arg Pro Gly Leu Val Ala Pro Ala Pro Leu Ala Gln
340 345 350

Glu Arg Glu Glu Asp Asp Glu Asp Asp Trp Asp Glu Glu Asp Asp Trp
355 360 365

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 12 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

Met Ala Glu Met Lys Thr Asp Ala Ala Thr Leu Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 396 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

GATCTCCGGC GACCTGAAAA CCCAGATCGA CCAGGTGGAG TCGACGGCAG GTTCGTTGCA	60
GGGCCAGTGG CGCGGCGCGG CGGGGACGGC CGCCCAGGCC GCGGTGGTGC GCTTCCAAGA	120
AGCAGCCAAT AAGCAGAAGC AGGAACTCGA CGAGATCTCG ACGAATATTG GTCAGGCCGG	180
CGTCCAATAC TCGAGGGCCG ACGAGGAGCA GCAGCAGGCG CTGTCCTCGC AAATGGGCTT	240
CTGACCCGCT AATACGAAAA GAAACGGAGC AAAAACATGA CAGAGCAGCA GTGGAATTTC	300
GCGGGTATCG AGGCCGCGGC AAGCGCAATC CAGGGAAATG TCACGTCCAT TCATTCCCTC	360
CTTGACGAGG GGAAGCAGTC CCTGACCAAG CTCGCA	396

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 80 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

Ile Ser Gly Asp Leu Lys Thr Gln Ile Asp Gln Val Glu Ser Thr Ala
 1 5 10 15

Gly Ser Leu Gln Gly Gln Trp Arg Gly Ala Ala Gly Thr Ala Ala Gln
 20 25 30

Ala Ala Val Val Arg Phe Gln Glu Ala Ala Asn Lys Gln Lys Gln Glu
 35 40 45

Leu Asp Glu Ile Ser Thr Asn Ile Arg Gln Ala Gly Val Gln Tyr Ser
 50 55 60

Arg Ala Asp Glu Glu Gln Gln Gln Ala Leu Ser Ser Gln Met Gly Phe
 65 70 75 80

(2) INFORMATION FOR SEQ ID NO:118:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 387 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

GTGGATCCCG ATCCCGTGTT TCGCTATTCT ACGCGAACTC GGCGTTGCC C TATGCGAAC A	60
TCCCAGTGAC GTTGCCTTCG GTCGAAGCCA TTGCCTGACC GGCTTCGCTG ATCGTCCGCG	120
CCAGGTTCTG CAGCGCGTTG TTCAGCTCGG TAGCCGTGGC GTCCCATT T TGCTGGACAC	180
CCTGGTACGC CTCCGAACCG CTACCGCCCC AGGCCGCTGC GAGCTTGGTC AGGGACTGCT	240
TCCCCCTCGTC AAGGAGGGAA TGAATGGACG TGACATTTCC CTGGATTGCG CTTGCCGCGG	300
CCTCGATAACC CGCGAAATTC CACTGCTGCT CTGTCATGTT TTTGCTCCGT TTCTTTCGT	360
ATTAGCGGGT CAGAAGCCCA TTTGCGA	387

150

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 272 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

CGGCACGAGG ATCTCGGTTG GCCCAACGGC GCTGGCGAGG GCTCCGTTCC GGGGGCGAGC	60
TGCGCGCCGG ATGCTTCCTC TGCCCGCAGC CGCGCCTGGA TGGATGGACC AGTTGCTACC	120
TTCCCGACGT TTCTGTTCGGT GTCTGTGCGA TAGCGGTGAC CCCGGCGCGC ACGTCGGGAG	180
TGTTGGGGGG CAGGCCGGGT CGGTGGTTCG GCCGGGGACG CAGACGGTCT GGACGGAACG	240
GGCGGGGGTT CGCCGATTGG CATCTTGCC CA	272

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

Asp Pro Val Asp Ala Val Ile Asn Thr Thr Cys Asn Tyr Gly Gln Val			
1	5	10	15
Val Ala Ala Leu			
20			

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

Ala Val Glu Ser Gly Met Leu Ala Leu Gly Thr Pro Ala Pro Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 19 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

Ala Ala Met Lys Pro Arg Thr Gly Asp Gly Pro Leu Glu Ala Ala Lys
1 5 10 15
Glu Gly Arg

(2) INFORMATION FOR SEO ID NO:123:

(1) SEQUENCE CHARACTERISTICS:

- SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

Tyr Tyr Trp Cys Pro Gly Gln Pro Phe Asp Pro Ala Trp Gly Pro
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 14 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

Asp Ile Gly Ser Glu Ser Thr Glu Asp Gln Gln Xaa Ala Val
1 5 10

(2) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 13 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Ala Glu Glu Ser Ile Ser Thr Xaa Glu Xaa Ile Val Pro
1 5 10

(2) INFORMATION FOR SEQ ID NO:126:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

Asp	Pro	Glu	Pro	Ala	Pro	Pro	Val	Pro	Thr	Thr	Ala	Ala	Ser	Pro	Pro
1				5					10					15	
Ser															

(2) INFORMATION FOR SEQ ID NO:127:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

Ala	Pro	Lys	Thr	Tyr	Xaa	Glu	Glu	Leu	Lys	Gly	Thr	Asp	Thr	Gly
1					5				10				15	

(2) INFORMATION FOR SEQ ID NO:128:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Asp Pro Ala Ser Ala Pro Asp Val Pro Thr Ala Ala Gln Leu Thr Ser
1 5 10 15

Leu Leu Asn Ser Leu Ala Asp Pro Asn Val Ser Phe Ala Asn
20 25 30

(2) INFORMATION FOR SEQ ID NO:129:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 22 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

Asp Pro Pro Asp Pro His Gln Xaa Asp Met Thr Lys Gly Tyr Tyr Pro
1 5 10 15

Gly Gly Arg Arg Xaa Phe
20

(2) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

Asp Pro Gly Tyr Thr Pro Gly
1 5

(2) INFORMATION FOR SEQ ID NO:131:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 10 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: /note= "The Second Residue Can Be Either a Pro or Thr"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

Xaa	Xaa	Gly	Phe	Thr	Gly	Pro	Gln	Phe	Tyr
1				5				10	

(2) INFORMATION FOR SEQ ID NO:132:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 9 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(ix) FEATURE:

(D) OTHER INFORMATION: /note= "The Third Residue Can Be Either a Gln or Leu"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

Xaa	Pro	Xaa	Val	Thr	Ala	Tyr	Ala	Gly
1				5				

(2) INFORMATION FOR SEQ ID NO:133:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 9 amino acids

- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

Xaa Xaa Xaa Glu Lys Pro Phe Leu Arg
1 5

(2) INFORMATION FOR SEQ ID NO:134:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

Xaa Asp Ser Glu Lys Ser Ala Thr Ile Lys Val Thr Asp Ala Ser
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:135:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 15 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

Ala Gly Asp Thr Xaa Ile Tyr Ile Val Gly Asn Leu Thr Ala Asp

1 5 10 15

(2) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

Ala Pro Glu Ser Gly Ala Gly Leu Gly Gly Thr Val Gln Ala Gly
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:137:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

Xaa Tyr Ile Ala Tyr Xaa Thr Thr Ala Gly Ile Val Pro Gly Lys Ile
1 5 10 15

Asn Val His Leu Val
20

Claims

1. A polypeptide comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

- (a) Asp-Pro-Val-Asp-Ala-Val-Ile-Asn-Thr-Thr-Cys-Asn-Tyr-Gly-Gln-Val-Val-Ala-Ala-Leu; (SEQ ID No. 120)
- (b) Ala-Val-Glu-Ser-Gly-Met-Leu-Ala-Leu-Gly-Thr-Pro-Ala-Pro-Ser; (SEQ ID No. 121)
- (c) Ala-Ala-Met-Lys-Pro-Arg-Thr-Gly-Asp-Gly-Pro-Leu-Glu-Ala-Ala-Lys-Glu-Gly-Arg; (SEQ ID No. 122)
- (d) Tyr-Tyr-Trp-Cys-Pro-Gly-Gln-Pro-Phe-Asp-Pro-Ala-Trp-Gly-Pro; (SEQ ID No. 123)
- (e) Asp-Ile-Gly-Ser-Glu-Ser-Thr-Glu-Asp-Gln-Gln-Xaa-Ala-Val; (SEQ ID No. 124)
- (f) Ala-Glu-Glu-Ser-Ile-Ser-Thr-Xaa-Glu-Xaa-Ile-Val-Pro; (SEQ ID No. 125)
- (g) Asp-Pro-Glu-Pro-Ala-Pro-Pro-Val-Pro-Thr-Thr-Ala-Ala-Ser-Pro-Pro-Ser; (SEQ ID No. 126)
- (h) Ala-Pro-Lys-Thr-Tyr-Xaa-Glu-Glu-Leu-Lys-Gly-Thr-Asp-Thr-Gly; (SEQ ID No. 127)
- (i) Asp-Pro-Ala-Ser-Ala-Pro-Asp-Val-Pro-Thr-Ala-Ala-Gln-Leu-Thr-Ser-Leu-Leu-Asn-Ser-Leu-Ala-Asp-Pro-Asn-Val-Ser-Phe-Ala-Asn; (SEQ ID No. 128) and
- (j) Ala-Pro-Glu-Ser-Gly-Ala-Gly-Leu-Gly-Gly-Thr-Val-Gln-Ala-Gly; (SEQ ID No. 136)

wherein Xaa may be any amino acid.

2. A polypeptide comprising an immunogenic portion of an *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative

substitutions and/or modifications, wherein said antigen has an N-terminal sequence selected from the group consisting of:

- (a) Asp-Pro-Pro-Asp-Pro-His-Gln-Xaa-Asp-Met-Thr-Lys-Gly-Tyr-Tyr-Pro-Gly-Gly-Arg-Arg-Xaa-Phe; (SEQ ID No. 129) and
- (b) Xaa-Tyr-Ile-Ala-Tyr-Xaa-Thr-Thr-Ala-Gly-Ile-Val-Pro-Gly-Lys-Ile-Asn-Val-His-Leu-Val; (SEQ ID No. 137), wherein Xaa may be any amino acid.

3. A polypeptide comprising an immunogenic portion of a soluble *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 1, 2, 4-10, 13-25, 52, 99 and 101 or a complement thereof under moderately stringent conditions.

4. A polypeptide comprising an immunogenic portion of a *M. tuberculosis* antigen, or a variant of said antigen that differs only in conservative substitutions and/or modifications, wherein said antigen comprises an amino acid sequence encoded by a DNA sequence selected from the group consisting of the sequences recited in SEQ ID Nos.: 26-51, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 26-51 or a complement thereof under moderately stringent conditions.

5. A DNA molecule comprising a nucleotide sequence encoding a polypeptide according to any one of claims 1-4.

6. An expression vector comprising a DNA molecule according to claim 5.

7. A host cell transformed with an expression vector according to claim 6.

8. The host cell of claim 7 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cells.

9. A pharmaceutical composition comprising one or more polypeptides according to any one of claims 1-4 and a physiologically acceptable carrier.

10. A pharmaceutical composition comprising one or more DNA molecules according to claim 5 and a physiologically acceptable carrier.

11. A pharmaceutical composition comprising one or more DNA sequences recited in SEQ ID Nos.: 3, 11 and 12; and a physiologically acceptable carrier.

12. A vaccine comprising one or more polypeptides according to any one of claims 1-4 and a non-specific immune response enhancer.

13. A vaccine comprising:

a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and

a non-specific immune response enhancer.

14. A vaccine comprising:

one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and

a non-specific immune response enhancer.

15. The vaccine of claims 12-14 wherein the non-specific immune response enhancer is an adjuvant.

16. A vaccine comprising one or more DNA molecules according to claim 5 and a non-specific immune response enhancer.

17. A vaccine comprising one or more DNA sequences recited in SEQ ID Nos.: 3, 11 and 12; and a non-specific immune response enhancer.

18. The vaccine of claims 16 or 17 wherein the non-specific immune response enhancer is an adjuvant.

19. A method for inducing protective immunity in a patient, comprising administering to a patient a pharmaceutical composition according to any one of claims 9-11.

20. A method for inducing protective immunity in a patient, comprising administering to a patient a vaccine according to any one of claims 12-18.

21. A fusion protein comprising two or more polypeptides according to any one of claims 1-4.

22. A fusion protein comprising one or more polypeptides according to any one of claims 1-4 and ESAT-6.

23. A pharmaceutical composition comprising a fusion protein according to claim 21 or 22 and a physiologically acceptable carrier.

24. A vaccine comprising a fusion protein according to claims 21 or 22 and a non-specific immune response enhancer.

25. The vaccine of claim 24 wherein the non-specific immune response enhancer is an adjuvant.

26. A method for inducing protective immunity in a patient, comprising administering to a patient a pharmaceutical composition according to claim 23.

27. A method for inducing protective immunity in a patient, comprising administering to a patient a vaccine according to claims 24 or 25.

28. A method for detecting tuberculosis in a patient, comprising:

- (a) contacting dermal cells of a patient with one or more polypeptides according to any one of claims 1-4; and
- (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.

29. A method for detecting tuberculosis in a patient, comprising:

- (a) contacting dermal cells of a patient with a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and
- (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.

30. A method for detecting tuberculosis in a patient, comprising:

- (a) contacting dermal cells of a patient with one or more polypeptides encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and
- (b) detecting an immune response on the patient's skin and therefrom detecting tuberculosis in the patient.

31. The method of any one of claims 28-30 wherein the immune response is induration.

32. A diagnostic kit comprising:

- (a) a polypeptide according to any one of claims 1-4; and
- (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.

33. A diagnostic kit comprising:

- (a) a polypeptide having an N-terminal sequence selected from the group consisting of sequences recited in SEQ ID NO: 134 and 135; and
- (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.

34. A diagnostic kit comprising:

- (a) a polypeptide encoded by a DNA sequence selected from the group consisting of SEQ ID Nos.: 3, 11 and 12, the complements of said sequences, and DNA sequences that hybridize to a sequence recited in SEQ ID Nos.: 3, 11 and 12; and
- (b) apparatus sufficient to contact said polypeptide with the dermal cells of a patient.

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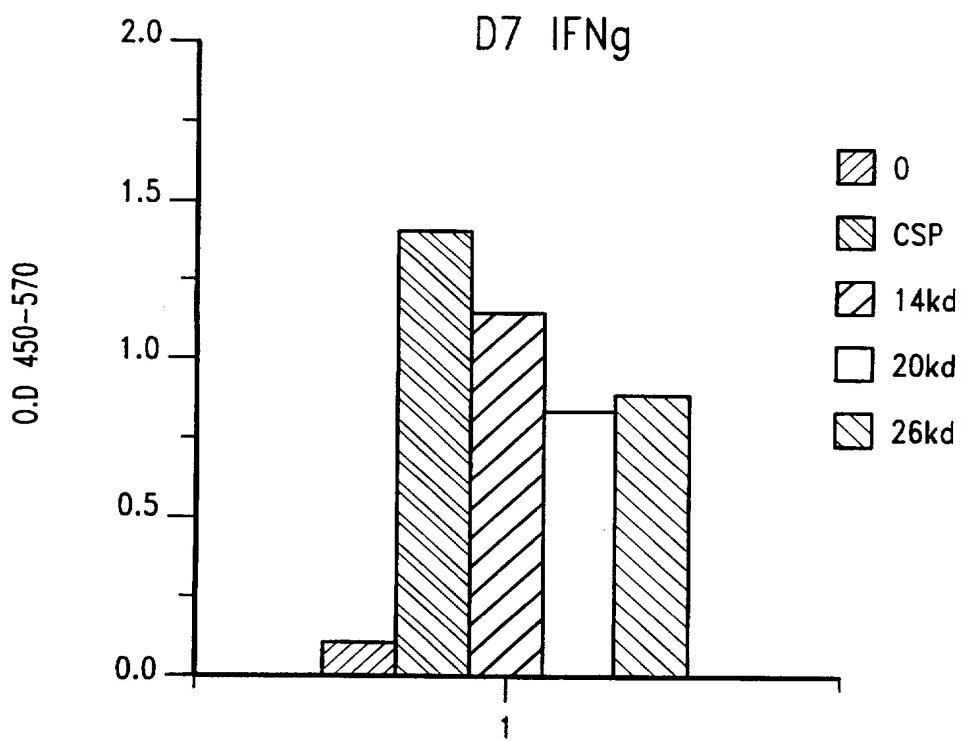
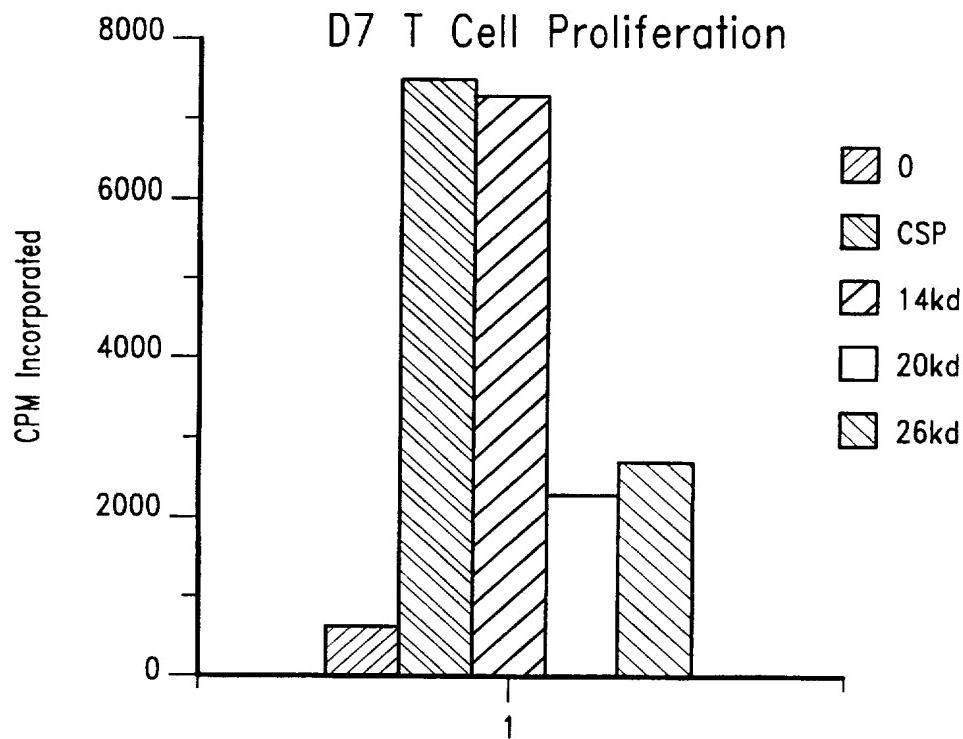


Fig. 1A
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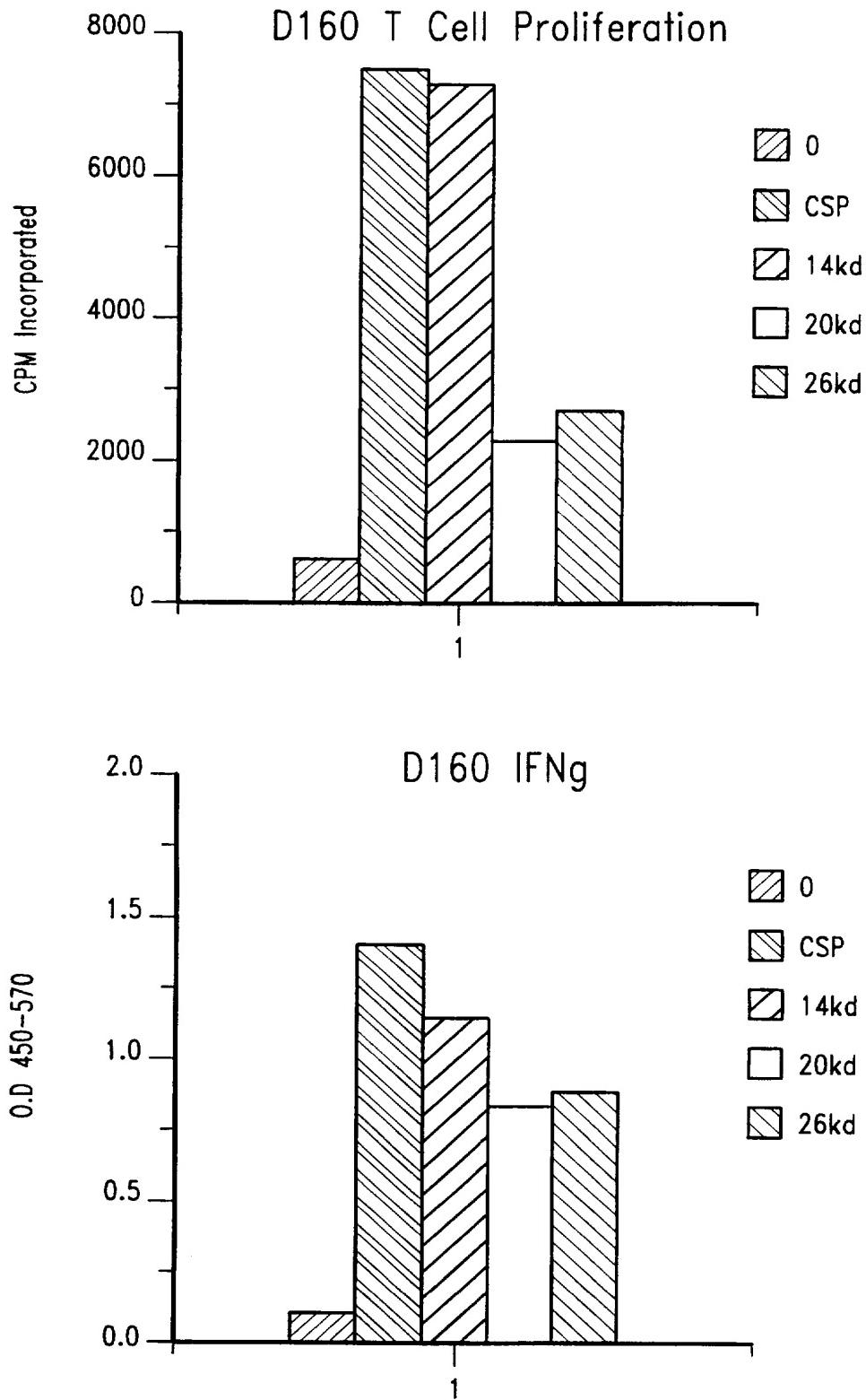


Fig. 1B

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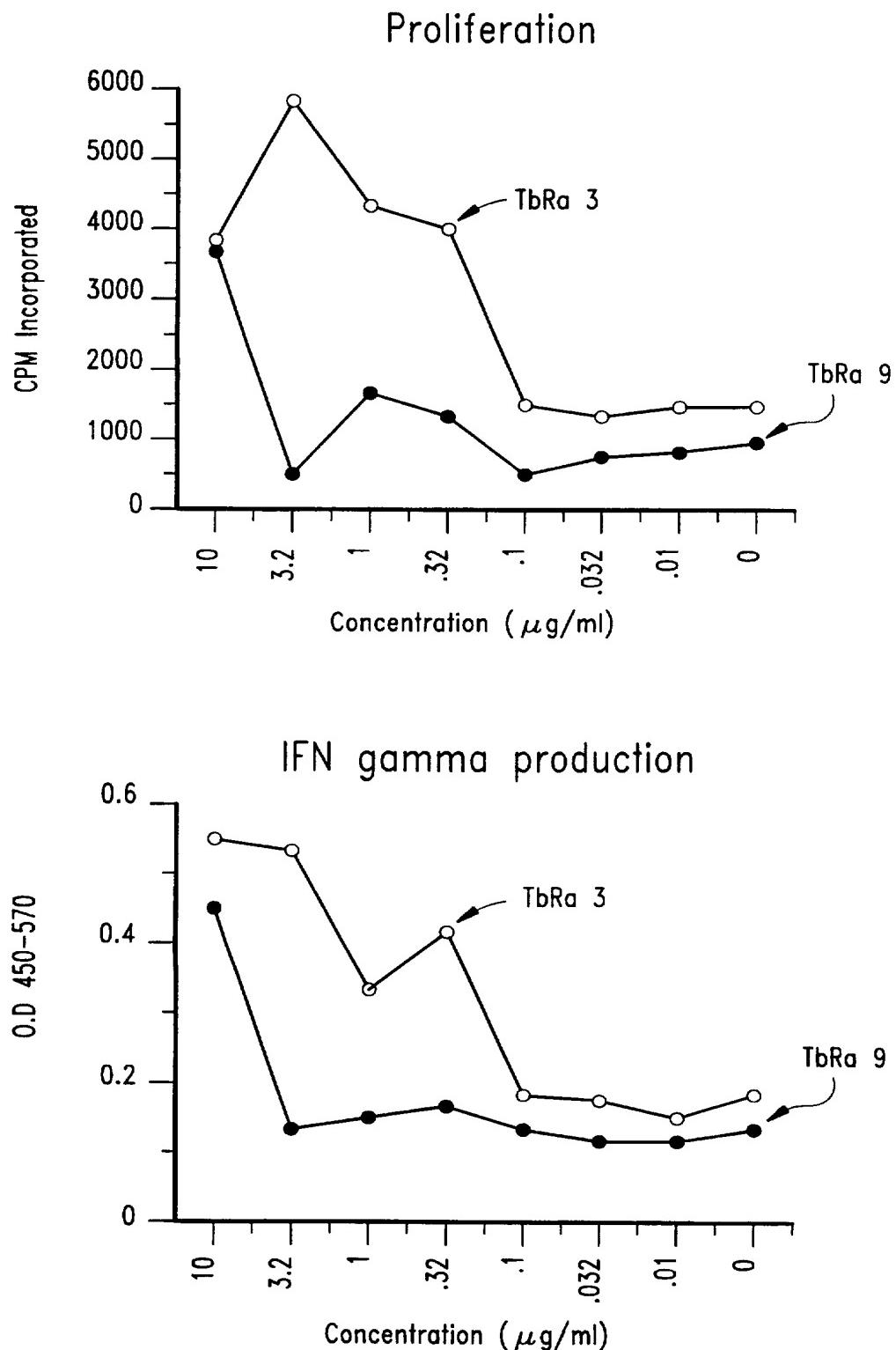


Fig. 2